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New Hope (and Challenges) for the Uncommon Lymphomas and for Multiple Myeloma

Jack W. Hsu, Jan S. Moreb, John R. Wingard

Mantle cell lymphoma (MCL) and peripheral T-cell lymphomas (PTCL) are rare subtypes of non-Hodgkin's lymphoma that together comprise <5% of all cases of NHL in adults. Both diseases are associated with poor outcomes with standard front line NLH chemotherapy. Additionally, investigations into new therapies for MCL and PTCL have been historically difficult due to their rarity.

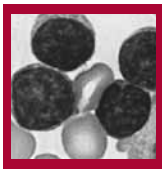
The development of large cooperative groups, however, has overcome some of the difficulty in studying these diseases. The Mantle Cell International Prognostic Index (MIPI) from the German Low Grade Lymphoma Study Group and the European Mantel Cell Lymphoma network and the Prognostic Index for PTCL (PIT) devised by the Italian Lymphoma Intergroup allows us to more accurately define the prognosis of these diseases. Therapeutically, there has been an explosion of new agents. In MCL, rituximab has found a role, not only in primary therapy, but also in maintenance. Pralatrexate and romidepsin were approved for the treatment of relapsed and refractory PTCL. Brentuxmab vedotin was approved for anaplastic large cell lymphoma in 2011. Bendamustine is emerging as an effective agent in frontline therapy for both diseases, with more agents under active investigation.

We are now entering an exciting era in the management of MCL and PTCL. As we learn more about MCL and PTCL, our ability to favorably alter the natural history of these diseases increases. Where there were once limited options, now there are a multitude of choices for the treatment.

Although rarity is hardly a problem for multiple myeloma (MM), in contrast to MCL and PTCL, heterogeneity of disease behavior is. There have been multiple, large randomized trials comparing various induction and maintenance regimens for both transplant eligible and transplant ineligible patients. Much has been learned about the importance of biological risk factors, the importance of achieving a complete remission, overlapping toxicities of certain drug combinations, and the effect of age on tolerance and benefits of therapy. Overall, one can say that the elderly, like the young, can benefit from similar therapeutic approaches; that not all patients benefit from maintenance; and that allogeneic HCT in its current form is still largely unsuccessful except in a select few. Some dogma has been discarded, and some new principles found. Yet, much remains to be learned.

This issue contains transcripts of two symposia, which address these issues; both were presented at the 2013 BMT Tandem Meetings in Salt Lake City, Utah. In Part I, Dr. Ginna Laport provided overviews of MCL and PTLD and discussed the role of hematopoietic cell transplant (HCT). Dr. Sonali Smith discussed non-transplant treatment options, including the role of new therapies for MCL and PTLD. In Part II, Dr. Sagar Lonial described how to categorize older aged individuals and reviewed the treatment trials and role of maintenance in older patients. Dr. Philip McCarthy reviewed the options of induction and maintenance therapies in HCT candidates. Finally, Dr. Amrita Krishnan provided a survey of studies of allogeneic HCT, to offer a perspective of what role this has for MM.

Clearly, much has been learned about multiple strategies of induction, the role of HCT, and maintenance strategies. There are new therapeutic options on the horizon for these tough diseases. Yet, the challenge of the still vexing and largely poorly characterized heterogeneity of disease behavior stands in the way of the clinician trying to decide what therapy is best for a given individual patient and when to treat and for how long.



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Blood and Marrow TRANSPLANTATION REVIEWS

Symposium Report

Multiple Myeloma Treatments for the Transplant-Eligible and Non–Transplant-Eligible Patient

Adapted from a continuing medical education symposium presented at the 2013 BMT Tandem Meetings on February 13, 2013, in Salt Lake City, Utah. This program is supported by an educational grant from Otsuka America Pharmaceutical, Inc.

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Needs Assessment

In 2012, the American Cancer Society estimated that 21,700 would be diagnosed with MM and that 10,710 individuals have died from the disease in the U.S. The 5-year survival rate is approximately 40% and men are more likely than women to be diagnosed with the cancer.

Treatments for MM include chemotherapy, radiation therapy, surgery, and stem cell transplantation. However, in recent years, emerging therapeutic agents such as proteasome inhibitors (PIs) and immunomodulatory drugs (IDs) have challenged conventional treatment approaches. Although these recent developments in therapeutic options have improved patient survival, nearly all MM patients eventually relapse. The appropriate regimen for relapsed or refractory patients depends on the nature of their initial therapy, the degree of response and remission duration, the aggressiveness of the relapsed disease, and patient's profile data, such as age, performance status, and pre-existing medical toxicity. A survey of recent literature recommended that MM patients with indolent relapse be treated first with 2- or 3-drug combinations, while those with more aggressive relapse be treated with a combination with multiple active agents

Learning Objectives

Upon completion of the Part I (*Multiple Myeloma Treatments for the Transplant-Eligible and Non–Transplant-Eligible Patient*), participants should be able to:

- Assess the modalities for frontline treatment for patients who are not-eligible for transplantation for multiple myeloma.
- Evaluate new data on agents for primary and maintenance therapy in patients with multiple myeloma who are candidates for transplantation.
- Describe the findings of ongoing clinical trials

Target Audience

The program will be oriented to a targeted audience of physicians and medical care professionals specializing in hematology, oncology, hematology, and blood and marrow transplantation.

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John R. Wingard, MD, has no relevant financial relationships to disclose.

Jack W. Hsu has no relevant financial relationships to disclose.

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Amrita Y. Krishnan, MD, has been a speaker for Millenium: The Takeda Oncology Company, Celgene, and Onyx.

Introduction

For patients with multiple myeloma, treatment with high-dose therapy and autologous stem cell transplantation (HDT-ASCT) extends progression-free survival and overall survival compared with conventional therapies. When the age threshold of < 65 years is used to determine transplant eligibility, however, the majority of patients with multiple myeloma are considered ineligible for HDT-ASCT based on the assumption that older patients cannot tolerate therapy. Furthermore, most patients with multiple myeloma are excluded from participation in clinical trials involving HDT-ASCT when age-based inclusion criteria are used. Given the predominance of older adults within the multiple myeloma patient population—the median age at diagnosis is 70 years—new treatment options are needed in both the transplantation and non-transplantation settings.

Multiple Myeloma Management of Older Patients

Sagar Lonial, MD

Multiple myeloma is a malignancy that occurs most commonly in older adults. In the Surveillance, Epidemiology, and End Results (SEER) registry database, 65% of all patients with multiple myeloma (N = 74,826) are over the age of 65 years [1]. Although patient age is an important consideration for treatment, the definition of the "older" patient with multiple myeloma varies worldwide. In Europe, those aged > 65 years are often described as older patients. The age threshold of 65 years, however, is not an accurate reflection of biologic risk.

Within the transplantation community, the following scheme has emerged to describe patient age: younger (typically < 70 years), older (typically 70 to 77 years), and frail (≥ 78 to 80 years). Only the truly frail patients, or those older than approximately 80 years, are considered ineligible for high-dose therapy based on age alone. Even with revised definitions, however, age is a blunt tool for risk assessment. Compared with age-based categories, performance status is a more useful delineator of transplantation outcomes.

Patient Age, Access to Treatment, and Survival Trends

Over the last 20 years, significant gains in overall survival have been observed in patients with multiple myeloma, primarily as a result of new therapeutic interventions such as thalidomide, lenalidomide, bortezomib, and ASCT. The newest therapies have been offered only to the youngest patient groups, however, and subsequently the survival benefits have been limited to this narrow subset of patients. These trends are clearly illustrated in a recent analysis of the SEER database that evaluated in age-specific survival of patients with multiple myeloma from 1990–1992 to 2002–2004 [2].

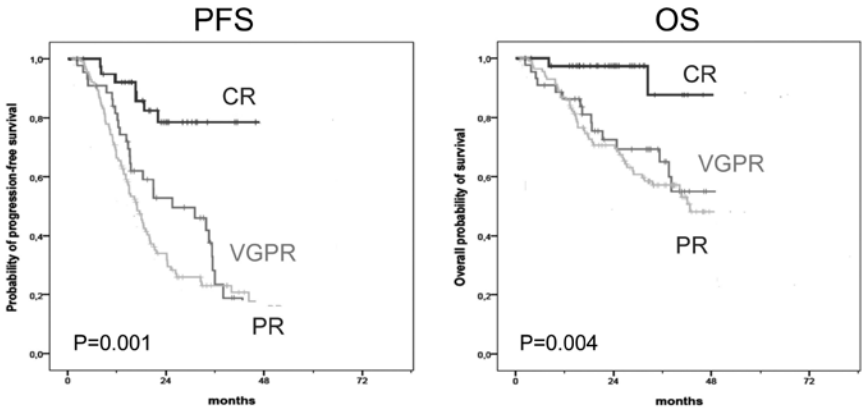

Figure 1. Complete response predicts improved progression-free and overall survival in elderly patients (> 75 years) with multiple myeloma treated with novel agents [3].

Across all patient subgroups, the 5-year overall survival rate increased significantly from 29% to 35% between 1990–1992 and 2002–2004 ($P < .001$). Likewise, 10-year survival for all patients increased from 11% to 17% ($P < .001$). The most dramatic improvements in overall survival, however, occurred among patients younger than 50 years. In this age group, the 5-year and 10-year survival rates reached 57% and 41%, respectively, in 2002–2004. For those aged 50 to 59 years, the 5-year and 10-year survival rates were 48% and 27%, respectively. By comparison, only modest improvements in survival were observed between 1990–1992 and 2002–2004 for patients aged 60 to 69 years, and for patients aged 70 and older, survival rates have remained essentially flat [2].

When offered to older patients with multiple myeloma, however, HDT-ASCT demonstrates significant survival benefits. In a recent study, Hailemichael and colleagues from from Emory University in Atlanta, Georgia, compared treatment outcomes in their institutional cohort of multiple myeloma patients with outcomes observed in the SEER database [1]. Among 901 myeloma patients who underwent HDT-ASCT at Emory, 167 patients (19%) were over the age of 65 years. The median overall survival was 20 months for all myeloma patients aged ≥ 65 years in the SEER database (n = 48,988), compared with 62 months among Emory transplant recipients aged ≥ 65 years ($P = .000$). The study investigators acknowledged the role of selection bias in this analysis, and indeed emphasized the important role of careful patient selection in planning appropriate treatment. A selection process that considers physiologic age as a determinant for transplantation eligibility, rather than chronologic age, does not preclude the elderly from the survival benefit associated with HDT-ASCT.

Treatment Goals for Older Patients

What is the rationale for approaching older patients differently? Older patients with multiple myeloma tend to be more sensitive to treatment-related toxicity. Older patients also have less physical reserve, which is necessary to withstand hospitalization and treatment-related morbidity. Despite these limitations, however, older patients with multiple myeloma have the

Table 1. Randomized Trials of MP versus MPT in Multiple Myeloma*

	GIMEMA Trial [4,5]	IFM 99-06 Trial [6]	IFM 01-01 Trial [7]	Nordic Trial [8]	HOVON Trial [9,10]
Median PFS, mo					
MP	15	18	19	14	9†
MPT	22	28	24	16	13
P	.0004	< .0001	.001	TTP‡	< .001
Median OS, mo					
MP	48	33	29	39	31
MPT	45	52	44	29	40
P	NS	.0006	.028	NS	.05

*MP indicates melphalan-prednisone; MPT, melphalan-prednisone-thalidomide; GIMEMA, Gruppo Italiano Malattie EMatologiche dell'Adulto; IFM, Intergroupe Francophone du Myéylome; HOVON, Haemato-Oncology Foundation for Adults in the Netherlands; PFS, progression-free survival; OS, overall survival.

†Event-free survival

‡Significant

same potential as younger patients to benefit from therapy. Regardless of age, effective therapy should induce high response rates without severe toxicity. Investigational therapies for multiple myeloma should also improve response and survival outcomes compared with standard comparator, irrespective of patient age.

A recent analysis of multicenter phase III trials illustrates the importance of achieving a complete response (CR) as a treatment goal for older patients with multiple myeloma [3]. The study included 1,175 patients with newly diagnosed multiple myeloma who were not eligible for HDT-ASCT because of older age (≥ 65 years) or comorbidities. The patients were enrolled in 1 of 3 European multicenter trials of novel melphalan-based treatment regimens: the Gruppo Italiano per lo Studio del Mieloma Multiplo (GISMM)-2001 trial of melphalan-prednisone (MP) versus melphalan-prednisone-thalidomide (MPT); the Dutch-Belgian Cooperative Trial Group for Hematology Oncology (HOVON) trial of MP versus MPT; and the Gruppo Italiano Malattie EMatologiche dell'Adulto (GIMEMA) MM0305 trial of melphalan-prednisone-bortezomib (VMP) versus melphalan-prednisone-thalidomide-bortezomib followed by bortezomib-thalidomide maintenance (VMPT-VT). After first-line treatment with MP (n = 332), MPT (n = 332), VMP (n = 257), or VMPT-VT (n = 254), the median follow-up was 29 months.

Regardless of treatment group, older patients who achieved a CR experienced a significantly longer progression-free survival ($P < .001$) and overall survival ($P < .001$) than those who achieved lesser responses, including a very good partial response (VGPR) or partial response (PR). In the subgroup of patients older than 75 years (n = 314), CR was also associated with a significant improvement in progression-free survival ($P < .001$) and overall survival ($P = .004$) compared with lesser responses (Figure 1). Thus, these findings demonstrate the clear association between CR to first-line treatment and favorable long-term outcomes. These findings also support the use of novel melphalan-based regimens to achieve maximal response in elderly patients with multiple myeloma, including patients older than 75 years.

Melphalan-Based Induction Therapy

Between 2006 and 2009, a series of 5 randomized established melphalan-based induction therapy with MPT as the standard of care for patients with transplantation-ineligible multiple myeloma (Table 1) [4-10]. In all 5 studies, treatment with MPT was superior to MP in terms of progression-free survival, time to progression, or both. In 2 studies, the Intergroupe Francophone du Myélome (IFM) 99-06 and IFM 01-01 trials, MPT was also superior to MP in terms of overall survival.

Melphalan, Prednisone, and Bortezomib

The international phase III VISTA trial evaluated the addition of bortezomib to standard treatment with MP (VMP) in 682 patients with newly diagnosed multiple myeloma who were older than 65 years and eligible for HDT-ASCT due to age or comorbidities [11]. The median age was 71 years, and 30% of patients were older than 75 years. Many patients had indicators of poor prognosis, including bone involvement (27%) or elevated serum levels of beta-2 microglobulin (33%) or albumin (60%).

Patients in the VMP arm (n = 337) received 9 consecutive 6-week cycles of bortezomib 1.3 mg/m^2 given twice weekly on days 1, 4, 8, 11, 22, 25, 29, and 32 during the first 4 treatment cycles and bortezomib 1.3 mg/m^2 once weekly on days 1, 8, 22, and 29 during cycles 5 through 9. Patients in both groups received oral melphalan 9 mg/m^2 and prednisone 60 mg/m^2 once daily on days 1 through 4 of each cycle. All patients continued therapy until disease progression or unacceptable toxicity, for a total of 9 cycles (54 weeks). The primary endpoint was time to progression.

VISTA: Survival Benefits Across Age Groups

The VISTA trial was stopped early when an interim analysis showed a significant survival advantage with VMP. After 16.3 months of follow-up, median overall survival was not reached in either arm. With 45 deaths in the VMP arm and 76 deaths in the MP arm, treatment with VMP reduced the risk of death by 39% (hazard ratio [HR], 0.61; $P = .008$). An analysis of survival outcomes by age showed consistent benefits with VMP across all age groups. The 2-year overall survival favored VMP compared with MP among patients younger than 75 years (84% versus 74%, respectively), and for those aged 75 and older (79% versus 60%, respectively).

Bortezomib also prolonged disease progression, regardless of patient age. The median time to progression was 24.0 months in the VMP arm and 16.6 months in the MP arm (HR, 0.48; $P < .001$). Grade 3 adverse events were significantly more common in the VMP group than in the MP group (53% versus 44%; $P = .02$), but there were no significant differences in grade 4 events (28% versus 27%) or treatment-related deaths (1% versus 2%).

VISTA: Sustained Survival Benefits with Long-Term Follow-Up

In 2013, San Miguel and colleagues reported the final analysis of the VISTA trial, showing a persistent overall survival benefit with VMP in patients with previously untreated multiple myeloma [12]. After a median follow-up of 60 months, treatment with VMP was associated with a 31% reduction in the risk of death (HR, 0.695; $P < .001$). The median overall survival was 56.4 months in the VMP group and 43.1 months in the MP group, representing a gain of 13.3 months in overall survival with the addition of bortezomib to the melphalan-based induction regimen. The long-term analysis also

showed a consistent survival benefit with VMP across patient subgroups, including patients aged 75 years or older.

The final analysis of the VISTA trial also examined subsequent therapy and outcomes following the use of salvage therapy. During the follow-up period, 63% of patients in the VMP group and 73% of those in the MP group received subsequent therapy. The time to next therapy was longer with VMP (30.7 months) than with MP (20.5% months; HR, 0.557; $P < .001$). Despite this difference, median overall survival from the start of subsequent therapy was similar in the VMP and MP groups (28.1 months versus 26.8 months, respectively; HR, 0.914). The addition of bortezomib to MP induction therapy did not appear to increase the risk of secondary hematologic malignancies or solid tumors, or raise any additional safety signals in this long-term follow-up analysis.

Melphalan, Prednisone, and Lenalidomide

Lenalidomide is also emerging as a potential add-on agent that can improve outcomes compared with standard melphalan-based induction therapy for elderly patients with newly diagnosed multiple myeloma. The phase III MM-015 trial evaluated the safety and efficacy of induction therapy with melphalan-prednisone-lenalidomide (MPR) followed by lenalidomide maintenance therapy (MPR-R), as compared with MPR or MP without maintenance therapy, in patients aged 65 years or older with newly diagnosed multiple myeloma who were ineligible for HDT-ASCT [13].

The multicenter, randomized, double-blind MM-015 trial enrolled 459 patients from 82 centers in Europe, Australia, and Israel. Patients were randomly assigned to 1 of 3 treatment arms: MPR-R, which consisted of 9 cycles of MPR—melphalan 1.8 mg/kg on days 1 through 4; prednisone 2 mg/kg on days 1 through 4; and lenalidomide 10 mg/day on days 1 through 21 of each 28-day cycle—followed by lenalidomide maintenance therapy until relapse or disease progression (n = 152); MPR induction followed by placebo maintenance (n = 153); or standard MP induction followed by placebo maintenance (n = 154). The primary endpoint was progression-free survival.

After a median follow-up of 30 months, the MPR-R regimen was associated with a highly significant 60% reduction in the risk of progression compared with standard MP induction therapy (HR, 0.40; $P < .001$). Treatment with MPR-R also significantly reduced the risk of progression compared with MPR (HR, 0.49; $P < .001$), illustrating the important role of the lenalidomide maintenance component of MPR-R in delaying disease progression. Overall, the median progression-free survival was 31 months in the MPR-R group, compared with 14 months in the MPR group and 13 months in the MP group. There was no difference between the MPR and MP groups in risk of progression (HR, 0.804; $P = .153$).

Unfortunately, the progression-free survival benefit was not consistent across age groups. In patients aged 65 to 75 years, treatment with MPR-R significantly reduced the risk of progression compared with MPR (HR, 0.48; $P < .001$) or MP (HR, 0.30; $P < .001$), but not in those older than aged 75 years. In patients older than 75 years of age, the median progression-free survival was 19 months in the MPR-R group, 12 months in the MPR group, and 15 months in the MP group. Statistical tests for the heterogeneity of treatment effects confirmed a significant treatment-by-age interaction ($P = .001$).

Summary: Melphalan-Based Induction Therapy

No head-to-head trials to date have demonstrated the superiority of one melphalan-based induction regimen over another in older patients with transplantation-ineligible multiple myeloma. Some patients appear to respond to proteasome inhibitor-based induction therapy, such as VMP, while others benefit from the addition of an immunomodulatory drug (IMiD) such as lenalidomide to standard MP therapy. In the absence of further clinical trial evidence, the selection of appropriate induction therapy for patients with multiple myeloma should be based on individual risk factors, treatment goals, and patient preferences.

Alternatives to Melphalan-Based Induction

Bortezomib, Thalidomide, and Prednisone

The VISTA trial established the superiority of VMP compared with MP alone in elderly patients with newly diagnosed multiple myeloma. The next important question was to clarify which agent was the optimal partner for bortezomib: an alkylating agent or an IMiD. To address this question, the Spanish Myeloma Group initiated a multicenter, randomized, 2-stage trial comparing VMP with bortezomib-prednisone-thalidomide (VTP) as indication therapy followed by maintenance with bortezomib-prednisone (VP) or bortezomib-thalidomide (VT) for up to 3 years [14]. The phase III GEM 05 > 65 trial enrolled 260 patients older than 65 years with newly diagnosed multiple myeloma.

Patients in the VMP arm (n = 125) received bortezomib 1.3 mg/m^2 twice weekly during the first 6-week cycle, followed by once weekly for 5 additional 5-week cycles, in combination with oral melphalan 9 mg/m^2 and prednisone 60 mg/m^2 once daily on days 1 through 4 of each cycle. Patients in the VTP arm (n = 128) received the same schedule of bortezomib and prednisone, but in place of melphalan they received thalidomide 100 mg/day. Following induction, 178 patients were randomized to maintenance therapy with VP or VT. Maintenance therapy consisted of a standard cycle of bortezomib 1.3 mg/m^2 twice weekly every 3 months given in combination with continuous thalidomide 50 mg/day or prednisone 50 mg on alternate days.

Responses after induction were rapid in both treatment arms. For all patients, the median time to achieving first response was 1.6 months. In the intent-to-treat analysis, overall response rate was similar following induction with VMP or VTP (80% versus 81%, respectively). Moreover, only 2 patients in each arm progressed during induction therapy.

Maintenance therapy increased the mean CR rate for all patients from 25% after induction to 42%, with no apparent differences between treatment groups. The median time to achieve a CR was 4.4 months in the VMP arm and 4.9 months in the VTP arm. After a median duration of maintenance therapy of 13 months, there was a trend suggesting more favorable freedom from progression at 1 year with VT compared with VP (84% versus 71%; $P = .05$), but no difference in 1-year overall survival (92% versus 89%).

The toxicity profiles of VMP and VTP differed substantially. Patients in the VMP group were more likely than those in the VTP group to experience grade ≥3 neutropenia (37% versus 21%, respectively) and grade ≥3 infections (7% versus <1%). Conversely, patients treated with VMP induction therapy experienced less cardiac toxicity and peripheral neuropathy than patients in the VTP arm. Cardiac events in the VTP arm included cardiac failure (n = 5), atrial fibrillation (n = 2), hypotension (n = 2), myocardial infarction (n = 1), and atrioventricular blockage (n = 1). In summary, the GEM 05 > 65 trial showed that prolonged therapy improves the quality of response after induction therapy with VMP or VTP in elderly patients with newly diagnosed multiple myeloma.

Carfilzomib, Cyclophosphamide, and Dexamethasone

As an alternative to melphalan, cyclophosphamide has been used as an alkylating agent in patients with multiple myeloma. Carfilzomib is a novel, irreversible proteasome inhibitor that shows significant antitumor activity and favorable toxicity profile. At the 2012 American Society of Hematology (ASH) annual meeting, Palumbo and colleagues reported results from a phase II multicenter trial of carfilzomib, cyclophosphamide, and dexamethasone (CCd) in 34 patients aged 65 years and older with newly diagnosed multiple myeloma [15]. The median age was 70 years, and 21% of patients were older than 75 years.

All patients received 9 cycles of induction therapy with CCd, which consisted of cyclophosphamide (300 mg/m^2 orally on days 1, 8, and 15), dexamethasone (40 mg orally on days 1, 8, 15, and 22) and intravenous (IV) carfilzomib (20 mg/m^2 on days 1 and 2, and 36 mg/m^2 on days 8, 9, 15, and 16 of cycle 1; and 36 mg/m^2 on days 1, 2, 8, 9, 15, and 16 during cycles 2 through 9) every 28 days. Patients also received maintenance therapy with carfilzomib 36 mg/m^2 on days 1, 2, 15, and 16 every 28 days until disease progression or treatment intolerance. Nineteen patients were evaluable for response.

All patients (100%) achieved at least a PR after 9 cycles of induction therapy, and 77% of patients achieved a VGPR. In addition, the overall rate for near-CR (nCR), CR, or stringent-CR (sCR) was 53%, including 23% who achieved sCR. The responses were rapid, with a median time of 1 month to PR and 2 months to CR. No patients progressed or died after a median follow-up of 7.5 months.

Treatment with the cyclophosphamide-based induction regimen was well tolerated, with fewer hematologic adverse events than observed with melphalan-based combinations. The most common grade ≥3 hematologic adverse events were neutropenia (15%) and thrombocytopenia (5%). The combined rate of at least 1 grade ≥3 non-hematologic adverse event was 21%. The overall rate of treatment discontinuation was low (12%), with no discontinuations due to adverse events.

Lenalidomide and Dexamethasone

Patients with multiple myeloma have also been treated successfully with combination regimens that include no alkylating agents. The phase III Eastern Cooperative Oncology Group (ECOG) E4A03 trial compared lenalidomide plus high-dose dexamethasone (RD) with lenalidomide plus low-dose dexamethasone (Rd) in 445 patients with newly diagnosed multiple myeloma [16]. Patients in the RD arm (n = 223) received lenalidomide 25 mg/day on days 1 through 21 plus dexamethasone 40 mg on days 1 through 4, 9 through 12, and 17 through 20 every 28 days. By comparison, those in the Rd arm received the same dose of lenalidomide plus dexamethasone 40 mg on days 1, 8, 15, and 22 every 28 days. The primary endpoint was response rate at 4 months.

The E4A03 trial was suspended early after an interim analysis showed significantly better overall survival for patients treated with low-dose dexamethasone ($P < .001$). Overall survival in the RD and Rd arms was 87% and 96%, respectively, at 1 year, and 80% versus 91%, respectively, at 18 months. The survival benefit with low-dose dexamethasone was consistent across all patient groups defined by age. Among patients aged ≥ 65 years, the estimated 2-year survival rate was 67% in the RD group and 82% in the Rd group ($P = .009$).

The increased mortality risk associated with high-dose dexamethasone was attributed to disease progression and treatment-related toxicity. Indeed, treatment with RD was associated with an increased risk of death in the first 4 months compared with Rd (5% versus 0.5%; $P = .006$) and an increased risk of any grade ≥3 non-hematologic adverse events (49% versus 32%; $P < .001$), particularly infection (16% versus 6%; $P < .001$) or venous thromboembolism (25% versus 9%; $P < .001$). The E4A03 trial has important implications for the use of dexamethasone in patients with newly diagnosed multiple myeloma, with findings that favor low-dose treatment.

Bortezomib-Based Combination Therapy

The phase III UPFRONT trial is representative of studies in the frail elderly population of multiple myeloma patients treated in community-based cancer clinics [17]. The trial compared the efficacy and safety of 3 bortezomib-based combination regimens—bortezomib-dexamethasone (VD), bortezomib-thalidomide-dexamethasone (VTD), and VMP—in 502 patients with newly diagnosed multiple myeloma who were ineligible for transplantation due to age or comorbidities. The median patient ages in the VD, VTD, and VMP groups were 74.5 years, 73 years, and 72 years, respectively.

Patients in the VD group (n = 168) received bortezomib 1.3 mg/m^2 on days 1, 4, 8, and 11 of all 21-day cycles, plus dexamethasone 20 mg on days 1, 2, 4, 5, 7, 9, 11, and 12 of cycles 1 through 4, and days 1, 2, 4, and 5 of cycles 5 through 8. Patients in the VTD arm (n = 167) received the same doses of bortezomib and dexamethasone as in the VD group, plus thalidomide 100 mg daily. Patients in the VMP arm received the same dose of bortezomib, plus melphalan 9 mg/m^2 and prednisone 60 mg/m^2 on days 1 through 4 of every other treatment cycle. After completing induction therapy, patients were eligible for maintenance therapy with bortezomib 1.6 mg/m^2 on days 1, 8, 15, and 22 every 35 days for a maximum of 5 cycles.

The best confirmed response rates during induction and maintenance appeared to favor treatment with VTD. Among patients with the VTD group, 51% achieved a VGPR, compared with 37% in the VD group ($P = .0174$ versus VTD) and 40% in the VMP group (P = NS). The overall response rates in the VD, VTD, and VMP groups were 73%, 80%, and 69%, respectively.

After a median follow-up of 26 months, progression-free survival was comparable across treatment regimens, with no statistically significant differences between the 3 study groups. The 1-year progression-free survival rates in the VD, VTD, and VMP arms were 57.4%, 63.8%, and 67.3%, respectively.

Investigators also examined quality of life outcomes in the UPFRONT trial [18]. Regardless of treatment regimen, there was a trend for decreasing quality of life during induction therapy, followed by an improvement or stabilization in quality of life during the maintenance phase. In general, there was a trend for poorer quality of life in the VTD arm versus the VD and VMP arms.

Is Melphalan Needed During Induction?

For years, melphalan-based induction therapy has been the standard of care for patients with newly diagnosed multiple myeloma who were ineligible for transplantation due to older age, comorbidities, or other contraindications. Emerging data suggest favorable responses and duration when melphalan is replaced with cyclophosphamide or a non-alkylating agent. To date, however, there is no clinical trial evidence to demonstrate whether these alternatives provide equal or better survival outcomes compared with melphalan.

Findings from the UPFRONT trial indicate that overlapping toxicity and poor quality of life may limit the utility of VTD-based approaches in older patients. Moreover, the safety and tolerability profiles may be different in older versus frail patients, and these differences need to be better understood. Randomized trials comparing melphalan-based treatment with non-alkylator-based regimens are required to clarify the optimal approach to induction therapy in elderly patients with newly diagnosed multiple myeloma.

Maintenance Therapy

Several studies have addressed the question of whether there is a role for maintenance therapy in older adults with multiple myeloma who are ineligible for HDT-ASCT. As described above, the phase III MM-015 trial compared continuous lenalidomide (MPR-R) with placebo maintenance following MPR or MP induction therapy in patients aged ≥ 65 with newly diagnosed multiple myeloma [13]. In a landmark analysis of progression-free survival—i.e., measured from the pre-defined landmark of the end of induction therapy—maintenance lenalidomide reduced the risk of progression compared with MPR alone by 69% (HR, 0.314; $P < .001$) (Figure 2). Overall survival data from the MM-015 trial are forthcoming, but so far, these findings provide strong support for the use of maintenance therapy to prolong disease control.

Additional insight about the value of maintenance therapy comes from the phase III GEM 05 > 65 trial [14]. In this trial, overall survival at 2 years was similar across all 4 treatment cohorts, regardless of randomization assignment to induction therapy (VTP versus VMP) or maintenance therapy (VT versus VP). Based on the cumulative evidence from early studies of maintenance therapy, therefore, the optimal maintenance regimen was not well defined.

At the 2012 ASH Annual Meeting, Palumbo and colleagues presented new long-term findings from the GIMEMA MM0305 trial that demonstrate a clear survival benefit with thalidomide-based maintenance therapy [19]. The GIMEMA trial included 511 patients with symptomatic multiple myeloma who were aged 65 years or older (or < 65 years and transplantation-ineligible). Patients were randomly assigned to induction therapy with VMP or VMPT. Only those patients in the VMPT arm also received maintenance therapy with VT. Patients in the VMP induction therapy arm received no additional treatment.

The median follow-up in the updated analysis was 47.2 months. Treatment with VMPT induction therapy followed by VT maintenance prolonged both progression-free survival and overall survival compared with VMP induction alone. In a landmark analysis, progression-free survival at 4 years was 33% for patients in the VMPT-VT group, compared with 16% for those in the VMP group. The median progression-free survival was 31.5 months with VMPT-VT and 17.8 months with VMP.

Several measures of overall survival also support the use of maintenance therapy. The 5-year overall survival rate was 61% in the VMPT-VT group, compared with 51% in the VMP group. These findings represent a 30% reduction in the risk of death for patients who received VT maintenance therapy (HR, 0.70; $P = .01$). Moreover, a landmark analysis of overall survival, measured from the start of maintenance therapy, shows consistent findings in favor of VMPT-VT compared with VMP (HR, 0.63; $P = .006$). Once patients have experienced disease relapse, overall survival was similar in both treatment arms. Measured from the time of relapse, the median overall survival was 27.8 months in the VMPT-VT group and 27.3 months in the VMP group ($P = .63$). This suggests that the upfront survival gain is a true advantage, with no detriment in survival time following relapse.

The GIMEMA MM0305 trial was the first trial to show an improvement in overall survival compared with standard melphalan-based induction therapy in older patients with multiple myeloma, with the benefit largely attributed to maintenance therapy with VT.

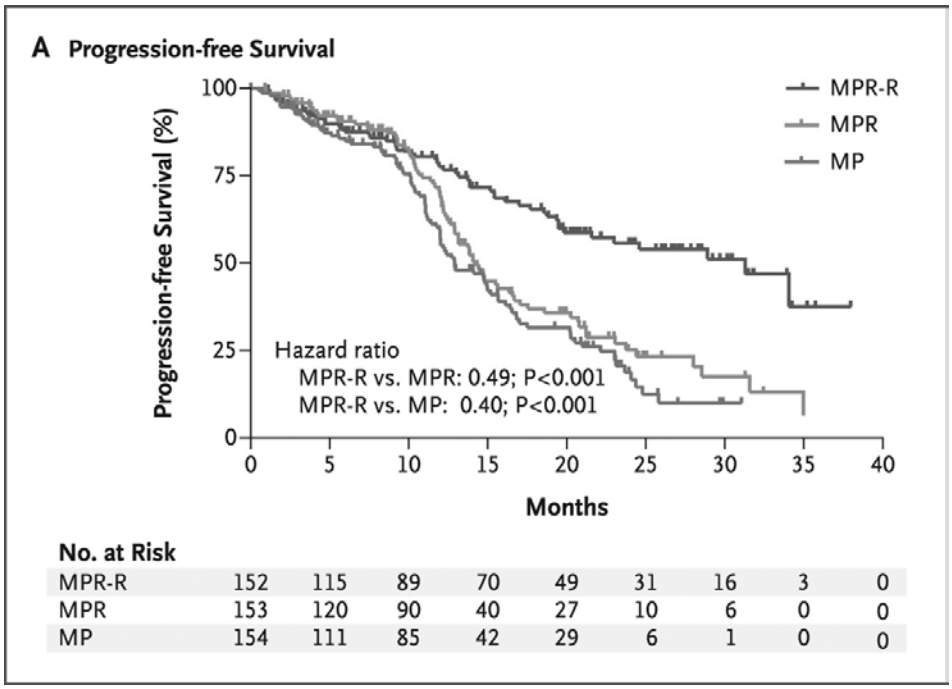

Figure 2. Improved progression-free survival with continuous lenalidomide [13].

Summary

When comparing options for first-line therapy in older patients with multiple myeloma, the potential depth of response and adverse event profile should be weighed carefully. To date, there is no consensus on the "best" regimen for patients who are ineligible for transplantation due to older age, comorbidities, or other contraindications because patient populations have been heterogenous across studies. Combination induction regimens that include melphalan or an alternative alkylator continue to appear in evidence-based recommendations for the treatment of older patients with newly diagnosed multiple myeloma. Recent evidence suggests that maintenance therapy in older patients can improve overall survival, and thus this treatment approach should be considered where appropriate.

Primary and Maintenance Therapy for Multiple Myeloma Transplant Candidates

Philip McCarthy, MD

Considerations for Frontline Treatment Selection

For patients with newly diagnosed multiple myeloma, the choice of frontline therapy should maximize the likelihood of response while considering the potential for treatment toxicity. In 2012, Ludwig and colleagues proposed an algorithm to guide the selection of frontline treatment of multiple myeloma (Figure 1) [20]. The first step in treatment selection is determining the eligibility for ASCT based on a range of baseline clinical and biologic factors [20]. These factors include age; comorbidities (renal, pulmonary, hepatic, cardiac, bone marrow); International Staging System (ISS) stage; cytogenetic aberrations by fluorescent in situ hybridization (FISH), such as t(4: 14), del 17p del 1q, t(14:16), t(14:20); gene expression profiling (GEP) signatures, such as those assessed by the 70-gene signature (GEP-70) or the EMC-92 gene model; extramedullary disease; plasma cell leukemia; and other unfavorable prognostic factors such as high lactate dehydrogenase (LDH), anemia, and bone disease.

Evolving Options for Induction Therapy

For transplantation-eligible patients, options for induction therapy include a range of 2-drug and 3-drug combinations with demonstrated activity in multiple myeloma [21]. Commonly used regimens include bortezomib, thalidomide and dexamethasone (VTD); lenalidomide, bortezomib, and dexamethasone (RVD); liposomal doxorubicin, bortezomib, and dexamethasone (DVD); cyclophosphamide, bortezomib, and dexamethasone (CVD); RD; and Rd. Combinations that incorporate newer agents tend to show improved outcomes, with rapid, frequent, and deep responses in patients with newly diagnosed multiple myeloma [21].

Measuring Response to Frontline Therapy

An analysis from the Medical Research Council Myeloma IX trial shows that the depth of response predicts outcomes following consolidation and maintenance therapy after HDT-ASCT [22]. Rawstron et al measured minimal residual disease (MRD) using muliparameter flow cytometry in divergent patient populations, including younger patients treated with HDT-ASCT and older patients treated with less intensive regimens. In the first cohort of 711 younger patients treated with cyclophosphamide, vincristine, doxorubicin, and dexamethasone (CVAD) or cyclophosphamide, thalidomide, and dexamethasone (CTD) induction therapy and high-dose melphalan, MRD was detected in 66% of patients at day 100 posttransplantation, and was highly predictive of worse outcomes. The median progression-free survival was 21 months in MRD-positive patients and 39 months in MRD-negative patients ($P = .0001$). Progression-free survival was particularly favorable among patients who were MRD-negative at the end of induction therapy (46 months; $P = .0015$ versus MRD-positive patients).

In the MRC Myeloma IX trial, investigators also evaluated the effect of maintenance therapy on the predictive utility of MRD. When maintenance regimens were taken into account, the shortest progression-free survival was observed in patients who were MRD-positive and received no maintenance therapy. By comparison, the longest progression-free survival was observed in patients who were MRD-negative and received thalidomide maintenance therapy ($P = .004$). The analysis also revealed a consolidation effect; 32% of MRD-positive patients who received maintenance thalidomide converted to MRD-negative status. Moreover, 80% of MRD-negative patients who received thalidomide maintenance remained MRD-negative, while only 46% of MRD-negative patients maintained their MRD-negative status without maintenance therapy.

In the second cohort of 510 transplantation ineligible patients, MRD was assessed following the completion of treatment with attenuated cyclophosphamide, thalidomide, and dexamethasone (CTDa) or melphalan and prednisone (MP). Only 8% of these patients achieved MRD-negative status, but MRD negativity was still able to predict superior progression-free survival in this small subgroup of patients ($P = .028$). Overall, data from the MRC Myeloma IX demonstrate that MRD assessment is effective for predicting treatment outcomes following both intensive and non-intensive therapy. These data also support the use of maintenance thalidomide to eradicate residual disease for many patients undergoing intensive treatment for multiple myeloma.

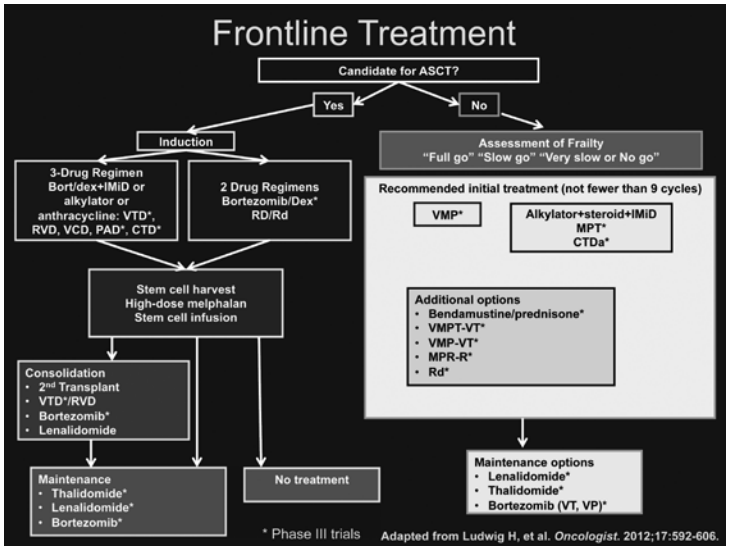

Figure 1. Frontline treatment for multiple myeloma. Adapted from [20]. CTD indicates cyclophosphamide, thalidomide, and dexamethasone; CTDa, attenuated CTD; EMA, European Medicines Agency; Dex, dexamethasone; IMiD, immunomodulatory drug; MPR-R, melphalan, prednisone, and lenalidomide plus lenalidomide maintenance; MPT, melphalan, prednisone, and thalidomide; RD, lenalidomide and high-dose dexamethasone; Rd, lenalidomide and low-dose dexamethasone; RVD, lenalidomide, bortezomib, and dexamethasone; VMP, bortezomib, melphalan, and prednisone; VMPT, VMP plus thalidomide; VP, bortezomib plus prednisone; VT, bortezomib plus thalidomide; VTD, bortezomib, thalidomide, and dexamethasone.

Bortezomib Maintenance Therapy

Bortezomib has been evaluated in a range of treatment settings, including induction therapy and post-ASCT consolidation therapy. The phase III HOVON-65/GMMG-HD4 trial evaluated whether bortezomib during induction and maintenance improves survival in younger patients with multiple myeloma [23]. The open-label trial enrolled 827 transplantation eligible patients aged 18 to 65 years (median age, 57 years) with newly diagnosed multiple myeloma.

Patients were randomly assigned to receive induction therapy with vincristine, doxorubicin, and dexamethasone (VAD; n = 414) or bortezomib, doxorubicin, and dexamethasone (PAD; n = 413), followed by high-dose melphalan and ASCT. Maintenance therapy consisted of thalidomide 50 mg once daily for patients in the VAD arm (n = 270) or bortezomib 1.3 mg/m^2 once every 2 weeks for those in the PAD arm (n = 229) for 2 years. Patients with an HLA-identical sibling proceeded to nonmyeloablative allogeneic hematopoietic stem cell transplantation (HSCT) after high-dose melphalan (n = 62) and did not receive maintenance therapy.

Progression-free survival was significantly better for patients who received PAD induction therapy followed by bortezomib maintenance compared with patients treated with VAD and thalidomide maintenance (HR, 0.75; P = .002). The 5-year overall survival was 61% in the PAD group and 55% in the VAD group. Multivariate analysis showed a survival advantage for the PAD/bortezomib regimen (HR, 0.77; P = .049).

Investigators also examined treatment outcomes in different patient subgroups defined by FISH abnormalities, such as del(13q14), t(4;14), and del(17p13). In this analysis, the superior outcome with bortezomib appears to be driven by patients with high-risk characteristics, including del(17p). For instance, in patients with del(17p13), treatment with PAD and bortezomib maintenance was associated with superior progression-free survival (HR, 0.47; P = .01) and overall survival (HR, 0.36; P = .003). By comparison, for patients without del(17p13), overall survival was identical in both treatment groups (HR, 0.96; P = .81).

The benefit of bortezomib was also more pronounced in the subgroup of patients with increased serum creatinine levels (> 2 mg/dL) at baseline. In this subgroup, treatment with PAD/bortezomib maintenance was associated with a dramatic improvement in progression-free survival (HR, 0.45; P = .004) and overall survival (HR, 0.33; P < .001) compared with VAD/thalidomide. Among patients with normal serum creatinine, progression-free survival remained superior in the PAD/bortezomib arm (HR, 0.80; P = .02), but overall survival was similar in both treatment groups (HR, 0.94; P = .94).

The HOVON-65/GMMG-HD4 trial demonstrated the utility of bortezomib during both induction and maintenance in newly diagnosed multiple myeloma. Future trials may clarify how much of the benefit of this approach can be attributed specifically to bortezomib maintenance.

Lenalidomide Maintenance

Lenalidomide has shown activity in the treatment of multiple myeloma at the time of diagnosis and at the time of relapse after chemotherapy or transplantation. Two recent phase III studies, the IFM 2005-02 trial and the Cancer and Leukemia Group B (CALGB) 100104 trial, evaluated the potential role of lenalidomide maintenance therapy in prolonging progression-free survival following successful ASCT [24,25].

IFM 2005-02 Study

The IFM 2005-02 study evaluated the efficacy and safety of lenalidomide maintenance after HDT-ASCT in patients with multiple myeloma [24]. The multicenter, randomized, double-blind, placebo-controlled trial enrolled 614 patients younger than 65 years of age who had been treated with first-line VD or VAD induction followed by ASCT within the previous 6 months and showed no evidence of disease progression. The median patient age was 55 years (range, 22 to 67 years). Patients were randomly assigned to consolidation treatment with lenalidomide 25 mg daily on days 1 through 21 of each 28-day cycle, for 2 cycles, followed by maintenance therapy with lenalidomide 10-15 mg daily until relapse (n = 307), or the same consolidation regimen followed by placebo maintenance (n = 307).

Lenalidomide maintenance therapy was associated with a substantial improvement in progression-free survival across all patient subgroups. The median progression-free survival was 41 months in the lenalidomide arm, compared with 23 months in the placebo arm (HR, 0.50; P < .001). The overall survival 4 years after randomization, however, was similar in the lenalidomide and placebo groups (73% versus 75%, respectively).

One potential limitation of maintenance therapy involves the risk of developing a second primary malignancy. In the IFM 2005-02 trial, patients in the lenalidomide group showed a significant increase in the incidence of second primary cancers compared with placebo. There were 32 second primary cancers in 26 patients in the lenalidomide group, representing an incidence of 3.1 per 100 patient-years, compared with 12 second primary cancers in 13 patients in the placebo group, for an incidence of 1.2 per 100 patient-years (P = .002). A multivariate analysis, lenalidomide maintenance therapy, age ≥ 55 years, male sex, and ISS stage III disease predicted an increased risk of developing a second primary malignancy.

CALGB 100104 Study

The CALGB 100104 trial also evaluated lenalidomide maintenance therapy in a slightly older patient population [25]. The trial enrolled 568 patients aged ≥ 70 years with multiple myeloma who had received any induction regimen of 2 to 12 months' duration and had stable disease or a marginal, partial, or complete response in the first 100 days after undergoing ASCT. The median age was 59 years (range, 29 to 71 years). Most patients (94%) received induction therapy with a regimen containing lenalidomide, thalidomide, or bortezomib, or a combination of the 3 agents. Between day 100 and day 110 after transplantation, 460 patients were randomly assigned to lenalidomide 10 mg/day (n = 231) or placebo (n = 229).

The primary endpoint was time to progression after transplantation. After meeting the primary endpoint in an early interim analysis, the CALGB 100104 trial was unblinded, allowing patients in the placebo group to cross over to lenalidomide. Of 128 patients without disease progression in the placebo group, 86 crossed over to lenalidomide maintenance therapy. Despite the crossover, the intent-to-treat analysis recognized these patients as members of the placebo cohort.

After a median follow-up of 34 months from the time of transplantation, lenalidomide maintenance significantly improved progression-free and overall survival in this patient population. The median time to progression was 46 months in the lenalidomide group, compared with 27 months in the placebo group (HR, 0.48; P < .001). Overall survival at 3 years was 88% in the lenalidomide group and 80% in the placebo group (HR, 0.62; P = .028).

Lenalidomide was also associated with an increased risk of second primary malignancies. In the lenalidomide group, 3.5% of patients were diagnosed with new hematologic

Table 1. The IFM 2005-02 and CALGB 100104 Trials of Lenalidomide Maintenance Therapy [24,25]*

Parameter	CALGB 100104	IFM 05-02
Induction regimen	Thalidomide- and lenalidomide-containing regimens (74%)	VAD (~52%) and VD (~44%)
Pre-ASCT consolidation	None	DCEP (~25%)
Number of ASCT	1	1 (79%), 2 (21%)
Post-ASCT consolidation before randomization	None	Lenalidomide: 25 mg daily, 3 of 4 weeks for 2 cycles
Median follow-up at un-blinding	~18 months	~33 months
Median follow-up from randomization	31 months	45 months
Dosing schedule	10 mg (between 5 to 15 mg)	10 mg (between 5 to 15 mg)
Time from first patient enrolled	78 months	62 months
Placebo patients crossed over to lenalidomide at un-blinding	Yes (86 of 128 eligible patients)	No
Secondary primary malignancies	~3-fold increase	~2.6-fold increase
Increase in AML/MDS	Yes	No
Increase in ALL/HL	No	Yes
Maintenance stopped	No	Yes, at a median of ~32 months

*IFM indicates Intergroupe Francophone du Myélome; CALGB, Cancer and Leukemia Group B; VAD, vincristine, doxorubicin, and dexamethasone; VD, bortezomib-dexamethasone; ASCT, allogeneic hematopoietic stem cell transplantation; DCEP, dexamethasone, cyclophosphamide, etoposide, and cisplatin; AML, acute myeloid leukemia; MDS, myelodysplastic syndrome; ALL, acute lymphoblastic leukemia; HL, Hodgkin's lymphoma.

cancers, and 4.3% of patients were diagnosed with new solid tumors (excluding nonmelanoma skin cancers). By comparison, in the placebo group, 0.4% of patients developed second primary hematologic malignancies, and 2.2% were diagnosed with second primary solid tumors.

To assess the influence of second primary cancers on progression-free and overall survival, investigators evaluated event-free survival as a post hoc endpoint. Overall, 92 of 231 patients in the lenalidomide group (40%) and 133 of 229 patients in the placebo group (58%) had progressive disease, died, or received a diagnosis of a second primary cancer ($P < .001$). The estimated hazard ratio for this combined endpoint was 0.53 (95% confidence interval [CI], 0.41 to 0.69), indicating a 47% reduction in risk of disease progression, death, or second primary malignancy among patients in the lenalidomide group.

Another post hoc subset analysis of outcomes by prior lenalidomide exposure revealed a potential advantage to lenalidomide induction therapy. The median time to progression was not yet reached in the subgroup of patients who received lenalidomide induction and lenalidomide maintenance, compared with 28 months for patients treated with lenalidomide induction and placebo maintenance. For patients with no prior exposure to lenalidomide, the median time to progression was 42 months in the lenalidomide maintenance group and 27 months in the placebo group. Overall survival outcomes showed a similar pattern in favor of lenalidomide induction. Among patients who received lenalidomide induction, 6% in the lenalidomide maintenance arm and 23% in the placebo arm have died ($P = .03$). Among those with no prior lenalidomide therapy, 20% in the lenalidomide maintenance arm and 23% in the placebo arm have died. Future trials are needed to confirm the advantage of lenalidomide induction therapy followed by lenalidomide maintenance after successful ASCT in patients with multiple myeloma.

Interpreting the IFM 2005-02 and CALGB 100104 Results

Although both the IFM 2005-02 and CALGB 100104 trials evaluated lenalidomide maintenance therapy in multiple myeloma, the trials had important differences that may explain the conflicting results [24,25]. Table 1 summarizes the major differences between these important trials.

Lenalidomide Maintenance After MPR or MEL200 Consolidation

Another phase III study evaluated conventional induction therapy with MPR versus tandem high-dose melphalan (MEL200), plus lenalidomide maintenance or no maintenance, in newly diagnosed multiple myeloma [26,27]. The multicenter study included 402 patients younger than 65 years. All patients received 4 cycles of induction therapy with Rd, which consisted of lenalidomide 25 mg on days 1 through 21 and low-dose dexamethasone 40 mg on days 1, 8, 15, and 22 every 4 weeks.

After induction, patients were randomly assigned to 1 of 2 consolidation regimens. Patients in the MPR group (n = 202) received 6 cycles of melphalan 0.18 mg/kg on days 1 through 4, prednisone 2 mg/kg on days 1 through 4, and lenalidomide 10 mg on days 1 through 21 every 28 days. Patients in MEL200 group (n = 200) received tandem melphalan 200 mg/m^2 with stem cell support. Following consolidation, patients underwent a second randomization to maintenance therapy with lenalidomide 10 mg on days 1 through 21 every 28 days until relapse (n = 198) or no maintenance therapy (n = 204).

In 2013, Boccadero and colleagues presented updated findings from the trial demonstrating the advantages of MEL200 induction therapy and lenalidomide maintenance [27]. After a median follow-up of 45 months from diagnosis, the median progression-free survival was 25 months for patients who received induction therapy with MPR and 39 months for those in the MEL200 group ($P = .0002$). The median progression-free survival was higher for those who received lenalidomide maintenance therapy than for those who received no maintenance (37.5 months versus 25.7 months, respectively; $P = .0008$). Measured from the time of diagnosis, the 4-year overall survival rates were similar for MPR and MEL200 (71% versus 72%; $P = .71$) and showed a trend in favor of lenalidomide maintenance compared with no maintenance ($P = .08$).

The updated analysis also measured outcomes after a median follow-up of 32 months from the start of maintenance therapy, independent of previous treatment. The median progression-free survival was 41 months for those in the lenalidomide group, compared with 18 months for no maintenance (P < .0001). From the start of maintenance therapy, the 3-year overall survival was 81% in the lenalidomide group and 72% for no maintenance (P = .04).

Ongoing Trials of Primary and Maintenance Therapy

Several questions remain regarding the optimal treatment of patients with newly diagnosed multiple myeloma. For instance, in the era of novel agents, it is unclear whether HDT-ASCT is still necessary in the management of multiple myeloma in younger patients. The role of consolidation therapy in the context of new IMiDs and proteasome inhibitors is also not well defined. Ongoing clinical trials are addressed some of these key research questions.

Phase III IFM/DFCI 2009 Study

The phase III IFM/Dana-Farber Cancer Institute (DFCI) 2009 trial will enroll approximately 1,000 patients with newly diagnosed multiple myeloma who are up to 65 years of age and candidates for HDT-ASCT. All patients will receive VRD induction for 3 cycles followed by stem cell collection. Patients will then be randomly assigned to immediate HDT-ASCT followed by lenalidomide maintenance for 12 months, or 5 more cycles of VRD and lenalidomide maintenance with transplantation offered at the time of relapse. The primary endpoint will be progression-free survival. The French study is one year of len maintenance and the US arm is len maintenance until progression. The US arm will enroll more patients, so the new accrual goal is 1m300 patients.

EMN 02 Trial

The international phase III European Myeloma Network (EMN) 02 trial will enroll approximately 1,570 patients younger than 65 years with previously untreated, symptomatic, ISS stage I-III multiple myeloma. The first randomization will assign patients to first-line treatment with VMP or high-dose melphalan and ASCT (MEL200). VCD induction, randomization to VMP, Single transplant or tandem transplant for a second randomization to VRD consolidation followed by maintenance with len or direct to len maintenance. For those patients assigned to immediate transplantation, the trial will also compare single versus tandem MEL200. The second randomization will compare VRD consolidation followed by lenalidomide maintenance versus lenalidomide maintenance alone. The primary endpoint will be progression-free survival.

BMT CTN 0702 STaMINA Trial

The phase III, multicenter, randomized Blood and Marrow Transplant Clinical Trials Network (BMT CTN) 0702 STaMINA trial will explore the role of consolidation after transplantation in approximately 750 patients aged up to 70 years with symptomatic multiple myeloma. All patients will undergo a standard single ASCT with the MEL200 protocol. After transplantation, patients will be randomly assigned to 1 of 3 treatment groups: second ASCT followed by lenalidomide maintenance; VRD consolidation plus lenalidomide maintenance; or straight to lenalidomide maintenance. In all treatment arms, maintenance therapy will include lenalidomide 10 mg daily for 3 months, followed by 15 mg daily for a total duration of 3 years. The primary endpoint will be 3-year progression-free survival.

Summary

Consolidation and maintenance therapy are effective treatment options that can improve responses and prolong progression-free, overall, and event-free survival in patients with transplantation eligible multiple myeloma. In particular, induction therapy with bortezomib, ASCT, and maintenance bortezomib improves survival outcomes in selected patients when compared to VAD induction, ASCT, and maintenance thalidomide. Based on current evidence, lenalidomide maintenance therapy appears to be the gold standard for improving progression-free and overall survival. The next phase of research in this area will focus on prognostic factors that will identify which patients are best treated with specific combination therapies and which patients should proceed to transplantation. Developing new treatment strategies for patients with high-risk disease is a major priority for multiple myeloma research.

Allogeneic Transplantation for Multiple Myeloma

Amrita Krishnan, MD

Multiple myeloma remains the leading indication for HSCT in the United States, with more than 5,000 transplantations performed each year [28]. The vast majority of transplantations for patients with multiple myeloma, however, are autologous. Between 2008 and 2011, patients with multiple myeloma received a total of 16,426 autologous transplantations at U.S. transplantation centers, compared with just 863 allogeneic transplantations [29]. The number of annual allogeneic transplantations peaked at more than 450 procedures per year in the early 2000s, in part due to the BMT CTN 0102 trial, but tapered to approximately 200 per year by 2010 [28].

In the era of novel agents, why choose allogeneic HSCT for patients with multiple myeloma? For some clinicians, selecting allogeneic transplantation reflects a philosophy of myeloma treatment that prioritizes CR and MRD as important treatment goals. In a retrospective study of patients undergoing various frontline regimens for multiple myeloma, including MP, MPT, VMP, and VMPT-VT, achieving a CR predicted a significant improvement in progression-free survival (P < .001) and overall survival (P < .001), irrespective of treatment strategy [3]. In another study of patients with multiple myeloma undergoing either autologous or allogeneic HSCT, achieving a molecular clinical remission prolonged the median relapse-free survival more than 3-fold from 35 months to 110 months (P < .005) [30].

New technologies for minimal residual disease monitoring, include polymerase chain reaction (PCR) and multicolor flow cytometry. Allogeneic HSCT can increase the likelihood of achieving MRD, although the potential limitations of this treatment strategy must be carefully weighed. Several recent trials of allogeneic HSCT in multiple myeloma have explored these options.

Table 1. Clinical Trials of Allogeneic HSCT in Patients with Multiple Myeloma*

Trial	ASCT Conditioning	Allogeneic HSCT Conditioning	High-Risk Patients	Standard-Risk Patients
IFM 99-03/IFM 99-04 [31]	NA	Flu/Bu/ATG	Yes	No
HOVON-50 [32]	Single ASCT → maintenance	TBI 2 Gy	Yes	Yes
Italian Trial [33,34]	Mel 140-200 tandem	TBI 2 Gy	Yes	Yes
PETHEMA/GEM-2000 [35]	Mel 140-200 CVB or Mel 200 tandem	Flu/Mel	Only patients not in CR	Only patients not in CR
EBMT [36]	Mel 200 single	Flu/TBI	Yes	Yes
BMT CTN 0120 [37]	Mel 200 tandem	TBI	Yes	Yes

*HSCT indicates hematopoietic stem cell transplantation; ASCT, allogeneic hematopoietic stem cell transplantation; IFM, Intergroupe Francophone du Myélome; NA, not applicable; Flu, fludarabine; Bu, busulfan; ATG, antitymocyte globulin; HOVON, Haemato-Oncology Foundation for Adults in the Netherlands; TBI, total body irradiation; Mel, melphalan; PETHEMA/GEM, Programa para el Estudio y la Terapéutica de las Hemopatías Malignas y Grupo Español de Mieloma; CVB, cyclophosphamide, etoposide, and carmustine; CR, complete remission.

Clinical Trials of Allogeneic Transplantation

To date, 6 major clinical trials have compared tandem autologous HSCT with or without maintenance therapy ("auto-auto") versus single autologous transplant followed by HLA-matched sibling non-myeloablative allogeneic HSCT ("auto-allo") for patients with multiple myeloma [31-37] (Table 1). The studies yielded conflicting results, with 2 trials demonstrating an advantage to the auto-allo protocol, and 4 trials showing no benefit to this approach compared with tandem ASCT.

How can these conflicting results be reconciled? When evaluating the evidence from clinical trials of allogeneic transplantation in multiple myeloma, several factors must be considered. Trials in the allogenic transplantation setting are not truly randomized. Instead, patients are assigned to treatment groups based on the availability of an HLA-matched sibling donor. In addition, efficacy outcomes are reported on an intent-to-treat basis, yet dropout rates between the first and second transplants vary widely across trials. Conditioning regimens also vary. Furthermore, the trials differ in their eligibility criteria, with some allowing only standard-risk patients and others enrolling patients with high-risk features. Finally, the length of follow-up varies across clinical trials.

IFM 99-03/IFM 99-04

In 1999, the IFM initiated 2 prospective clinical trials in patients aged 65 years or younger with newly diagnosed multiple myeloma [31]. All patients were classified as high risk, based on high β2-microglobulin levels (> 3 mg/L) or chromosome 13 deletion [del(13)] by FISH analysis. Patients with an HLA-identical sibling donor (n = 65) enrolled in the IFM99-03 trial, which evaluated dose-reduced allogeneic HSCT after a single melphalan-based autologous HSCT (MEL200). Patients with no available donor (n = 219) enrolled in the IFM99-04 trial and received tandem autologous transplantation, which included a second ASCT with dose-intensified MEL220.

After a median follow-up of 24 months, there was no difference in clinical outcomes between the treatment groups. The median event-free survival was 31.7 months in the IFM99-03 trial and 35 months in the IFM99-04 study (P = .35). Overall survival findings showed a trend in favor of the IFM99-04 protocol, but the difference did not reach statistical significance (P = .07). The median overall survival was 35 months for patients treated with autologous HSCT followed by dose-reduced allogeneic transplantation, compared with 47.2 months for patients treated with tandem autologous HSCT.

PETHEMA/GEM-2000 Trial

The Spanish PETHEMA/GEM-2000 trial compared transplantation strategies in 110 patients aged < 70 years with newly diagnosed multiple myeloma who failed to achieve at least near-CR after an initial ASCT [35]. Depending on the availability of an HLA-identical sibling donor, patients underwent a second ASCT (n = 85) or a reduced-intensity allograft (n = 25). Among patients who underwent a second ASCT, only 3% of those who received conditioning with cyclophosphamide, etoposide, and carmustine (BCNU) (CVB) achieved a CR, compared with 35% who received MEL200 conditioning (P < .001).

After a median follow-up of 5.2 years from the second transplantation, there was a trend toward longer median progression-free survival in favor of allogeneic HSCT (not reached) compared with tandem ASCT (31 months; P = .08). However, there was no difference between the reduced-intensity conditioning (RIC) allogeneic HSCT and second ASCT groups in terms of median event-free survival (19.6 months versus 26 months; P = .4) or median overall survival (not reached versus 58 months; P = .9). Overall survival at 5 years was similar for patients who received RIC allogeneic HSCT after an initial ASCT (60%) or those who received a second ASCT (61.8%).

BMT CTN 0102 Trial

The phase III BMT CTN 0102 trial also evaluated allogeneic HSCT with non-myeloablative conditioning after ASCT compared with tandem ASCT [37]. The trial enrolled 710 patients (aged < 70 years) from 37 transplantation centers in the United States. All patients had received at least 3 cycles of systemic therapy for multiple myeloma within the past 10 months. All patients underwent an autologous HSCT with MEL200 conditioning. Based on the availability of an HLA-matched sibling donor, patients were assigned to a second autologous transplantation with MEL200 conditioning (n = 484) or nonmyeloablative conditioning with 2 Gy total body irradiation (TBI) and allogeneic transplantation (n = 226). Patients in the tandem ASCT group were randomly assigned to thalidomide/dexamethasone maintenance or observation for 12 months. Patients with high-risk disease (n = 85), defined by elevated β2-microglobulin concentration and adverse cytogenetics, were excluded from the efficacy analysis.

The intent-to-treat analysis showed no difference in clinical outcomes after 3 years. The estimated 3-year progression-free survival was 43% in the auto-allo group, compared with 46% in the tandem ASCT group (P = .671). Overall survival at 3 years was also similar for patients treated with nonmyeloablative allogeneic HSCT following ASCT (77%) or tandem ASCT (80%: P = .191). Despite similar overall survival rates, the cumulative 3-year risk of treatment-related mortality was significantly

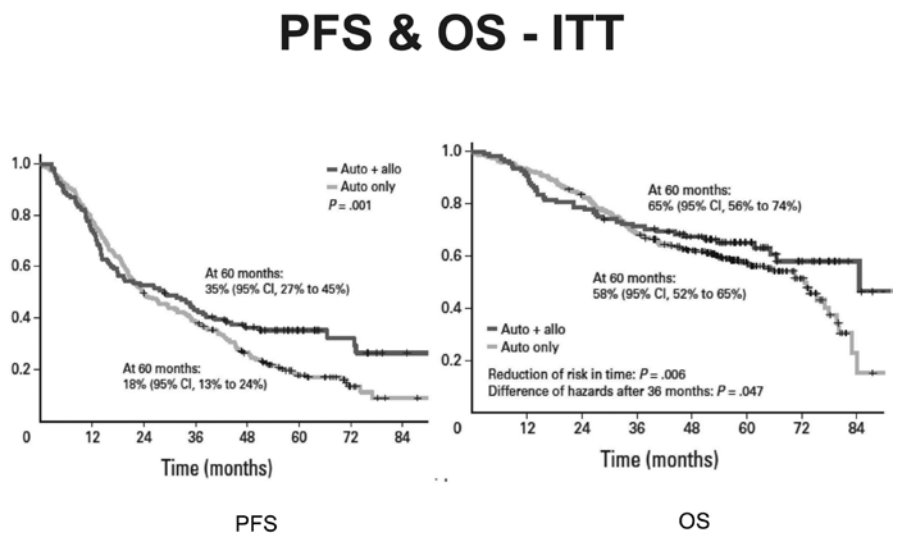

Figure 1. Improved progression-free and overall survival with auto-allo hematopoietic stem cell transplantation (HSCT) compared with auto-auto HSCT in multiple myeloma [36].

higher in the auto-allo group than in the auto-auto group (11% versus 4%; $P < .0001$). Within the tandem ASCT group, there was no difference in progression-free or overall survival with or without maintenance therapy, but the ability to tolerate the planned maintenance was poor, and the dropout rate was high.

In a separate analysis, Stadtmauer and colleagues evaluated outcomes from the BMT CTN 0102 trial in patients with high-risk multiple myeloma [38]. In this small subgroup of patients, findings were similar in both treatment groups. The 3-year progression-free survival rate was 40% in the auto-allo group and 33% in the auto-auto group ($P = .74$). The 3-year overall survival rate was 59% and 67%, respectively ($P = .46$).

HOVON-50 Donor versus No-Donor Analysis

In 2012, Lokhorst and colleagues performed a donor versus no-donor analysis (DvND) of patients enrolled in the HOVON-50 trial to approximate a randomized trial of transplantation strategies following first-line autologous HSCT [32]. The HOVON-50 trial was designed to evaluate the effect of thalidomide combined with ASCT and included 536 patients with transplantation eligible multiple myeloma. Of these, 260 patients met the following inclusion criteria for the DvND analysis: HLA typing of patient and all siblings; treatment in a transplantation center with a policy to include RIC allogeneic HSCT as part of first-line therapy; and receipt of an autologous HSCT after February 1, 2003.

The DvND study population included 122 patients with an HLA-identical sibling donor and 138 patients without an HLA-identical sibling donor. In the donor group, 15 patients received maintenance therapy following ASCT and 99 patients received an RIC allogeneic HSCT. In the no-donor group, 97 patients received post-ASCT maintenance therapy, and 3 patients underwent a second ASCT with MEL200. After a median follow-up of 77 months, there were no differences in clinical outcomes between the donor and no-donor groups. The 6-year progression-free survival rate was 28% for patients with an HLA-matched sibling donor and 22% for patients without a donor ($P = .19$). The 6-year overall survival rate was 55% in both groups ($P = .68$).

Italian Multicenter Trial

In 2011, Bruno and colleagues reported long-term follow-up findings from the first trial to show survival benefits with allogeneic HSCT compared with standard ASCT in patients with newly diagnosed multiple myeloma [33,34]. The Italian multicenter trial included 245 patients aged 65 years or younger with stage IIA-IIIB multiple myeloma. Of these, 162 patients had at least 1 sibling with HLA typing available. All patients received initial treatment with vincristine, doxorubicin, and dexamethasone, followed by melphalan and autologous HSCT. Patients with an HLA-identical sibling donor (n = 80) received nonmyeloablative TBI followed by allogeneic HSCT. Patients without an HLA-identical sibling (n = 82) received a second melphalan-based autograft.

The median follow-up in the long-term analysis was 7 years from the time of diagnosis. The intent-to-treat analysis showed a significant improvement in median overall survival for patients with HLA-identical sibling donors compared with the no-donor group (not yet reached versus 4.25 years, respectively; $P = .001$). Patients with HLA-matched sibling donors also experienced prolonged event-free survival compared with those without matched donors (2.8 years versus 2.4 years; $P = .005$).

The per-protocol analysis also showed a significant survival and disease-free advantage in favor of allografting. Median overall survival was not yet reached in the 58 patients who received a nonmyeloablative allograft after ASCT, compared with 5.3 years for the 46 patients who received 2 high-dose melphalan autografts ($P = .02$). The median event-free survival was 39 months in the auto-allo group and 33 months in the auto-auto group ($P = .02$).

EBMT Trial

Long-term findings from a study of 23 European Bone Marrow Transplantation (EBMT) centers also support the use of allogeneic HSCT in multiple myeloma [36]. The prospective multicenter trial enrolled 357 patients up to age 69 years with previously untreated multiple myeloma. Patients with an HLA-identical sibling donor (n = 108) were assigned to the auto-allo arm and received conditioning with 2 Gy TBI plus fludarabine 30 mg/m^2 daily for 3 days prior to allogeneic HSCT. Patients without a matched sibling donor (n = 249) were assigned to the autologous HSCT arm and permitted to undergo a single (n = 145) or tandem (n = 104) transplantation with standard MEL200 conditioning.

The intent-to-treat analysis showed a significant long-term benefit with allogeneic HSCT. At 60 months, the auto-allo protocol resulted in superior progression-free survival compared with autologous transplantation alone (35% versus. 18%; $P = .001$), as well as superior overall survival (65% versus 58%; $P = .001$) (Figure 1).

Ongoing Challenges in Allogeneic Transplantation

Improving transplantation outcomes will require strategies to reduce the risk of treatment-related mortality, reduce the incidence of

graft-versus-host disease (GVHD), and refine the definition of high-risk disease as it relates to transplantation eligibility.

Reducing the Risk of GVHD

The development of acute and chronic GVHD is a major challenge in the post-allograft setting. The HOVON 76 trial examined the role of lenalidomide maintenance initiated 1 to 6 months after first-line treatment with nonmyeloablative allogeneic HSCT in patients with multiple myeloma [39]. Patients were scheduled to receive lenalidomide 10 mg on days 1 to 21 of each 28-day cycle for a total of 24 cycles. After 2 cycles, however, 14 of 30 patients (47%) had to stop treatment, primarily due to the development of acute GVHD. Overall, 23 patients stopped treatment because of GVHD (43%), other adverse events (17%), or because of disease progression (17%). Only 3 patients (10%) were able to complete all 24 cycles of lenalidomide maintenance. The investigators concluded that lenalidomide maintenance after nonmyeloablative allogeneic HSCT is not feasible, given the high risk of inducing GVHD.

In 2013, Becker and colleagues described findings from another prospective phase I/II trial of lenalidomide maintenance therapy following allogeneic HSCT [40]. The trial included 30 patients with high-risk multiple myeloma, described as the presence of disease after autologous HSCT and/or plasmablastic morphology >2%, β2microglobulin ≥ 5.5 mg/L, or high-risk cytogenetics (hypodiploidy, del 13 by standard karyotyping, t(4;14), t(14;16), or del 17p). Patients were treated with lenalidomide 10 mg/day for 3 weeks every 28 days. The median time to starting lenalidomide was 96 days following allogeneic HSCT, and 34% of patients completed the full 12-month maintenance regimen. The most common reasons for treatment discontinuation were acute GVHD in 37% of patients and neutropenia in 10% of patients.

The immunomodulatory properties of bortezomib have also been evaluated as a potential option for GVHD prophylaxis. A recent phase II trial examined the use of a GVHD prophylaxis regimen that consisted of a short course of bortezomib on days 1, 4, and 7 posttransplantation plus standard tacrolimus and methotrexate in 45 patients with hematologic malignancies undergoing HLA-mismatched unrelated donor reduced-intensity allogeneic HSCT [41]. Patients treated with the GVHD prophylaxis regimen showed similar rates of non-relapse mortality, acute and chronic GVHD, and survival compared with historical controls of patients undergoing HLA-matched RIC allogeneic HSCT. The 180-day cumulative incidence of acute GVHD was 22%, and after 1 year, 29% of patients developed chronic GVHD. At 2 years, the cumulative risk of non-relapse morality was 11%, progression-free survival was 51%, and overall survival was 64%. In another study of 18 patients who received bortezomib maintenance therapy following reduced-intensity allogeneic HSCT, 1 patient developed acute GVHD, and 3 patients experienced an aggravation of existing GVHD [42].

Improving Patient Selection

Traditional definitions of high-risk multiple myeloma have relied on factors such as β2-microglobulin concentration and del(13) status. By refining the definition of high-risk disease, clinicians may be better able to identify the patients who are most likely to benefit from allogeneic HSCT after relapse from prior ASCT.

In a recent study, Kröger and colleagues demonstrated the potential role of auto-allo HSCT in overcoming the negative prognostic implications of del(17p13) and/or t(4;14) in patients with multiple myeloma [43]. The study included 73 patients who were treated with induction chemotherapy followed by MEL200 before undergoing autologous HSCT; 3 months later they received melphalan 140 mg/m^2 and fludarabine 180 mg/m^2 before allogeneic HSCT. According to FISH analysis, 16 patients had high-risk cytogenetic features, including del(17p13) and/or t(4;14). In the overall study population, 66% of patients achieved at least a near-CR, and 41% achieved a mCR, with no differences in the distribution of responses among patients based on cytogenetic profile. Patients with high-risk cytogenetics were equally likely as others to achieve CR, nCR, or mCR following the auto-allo protocol (P = .70).

The 5-year progression-free survival rate was 29% among all patients, with no difference between patients harboring high-risk cytogenetics and patients without the chromosomal abnormalities (24% versus 30%; P = .70). However, 5-year progression-free survival did vary substantially according to the level of remission achieved: 17% for PR, 41% for CR, 57% for mCR, and 85% for sustained mCR. Treatment with auto-allo HSCT, therefore, allows patients harboring del(17p13) and/or t(4;14) to achieve molecular remission and long-term freedom from disease.

Another recent study, however, demonstrated a significant survival advantage with second autologous HSCT compared with allogeneic HSCT in patients with relapsed multiple myeloma [44]. Using the CIBMTR database, investigators analyzed transplantation data from 137 patients who received a second autologous HSCT and 152 patients who received reduced-intensity or nonmyeloablative allogeneic HSCT after relapse from prior ASCT. Key baseline characteristics differed between the treatment groups. Patients who received a second ASCT were significantly older at the time of second transplantation than those in the allogeneic HSCT group (56 years versus 53 years; P < .001). The interval between first and second transplantation was also longer in the ASCT group than in the allogeneic HSCT group (30 months versus 23 months; P = .014).

In this analysis, a second autologous HSCT was associated with a significant improvement in 3-year overall survival rate compared with the auto-all approach (46% versus 20%; P < .001). Much of the difference was driven by a significantly higher risk of treatment-related mortality following allogeneic HSCT. The risk of treatment-related mortality in the auto-auto and auto-allo groups were 2% and 13%, respectively, at 12 months (P < .001), and 4% and 15%, respectively, at 60 months (P < .001). In a multivariate analysis, several factors independently predicted an increased risk of death, including treatment with allogeneic HSCT (HR, 2.38; P < .001), Karnofsky performance status < 90 (HR, 1.96; P < .001), and year of transplantation, 2004 or earlier (HR, 1.77; P < .001).

Summary

Multiple myeloma is an incurable yet highly treatable disease. Treatment with autologous HSCT is considered standard therapy for multiple myeloma, and remains the most common indication for transplantation among patients with hematologic malignancies. Compared with ASCT, allogeneic HSCT is less commonly used because of the high risk of treatment-related mortality. Advances in reduced-intensity and nonmyeloablative conditioning have tempered this risk, but challenges remain. Allogeneic transplantation can induce long-term disease remission in carefully selected patients with relapsed multiple myeloma, but its optimal use remains limited by acute and chronic GVHD. In the era of novel agents and other new treatment options for advanced multiple myeloma, improving the identification of patients who are most likely to benefit from allogeneic transplantation is a research priority.

ASBMT

Blood and Marrow TRANSPLANTATION REVIEWS

Symposium Report

Transplant and Non-Transplant Therapies for Mantle Cell Lymphoma and Peripheral T-Cell Lymphoma

Adapted from a continuing medical education symposium presented at the 2013 BMT Tandem Meetings on February 16, 2013, in Salt Lake City, Utah. This program is supported by an educational grant from Otsuka America Pharmaceutical, Inc.

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Needs Assessment

MCL accounts for approximately 6% of non-Hodgkin lymphoma cases. It is an aggressive B-cell lymphoma that typically affects men in their early 60s. MCL patients fall into two categories: those who experience a chronic/indolent course of the disease, and those who have a more fulminant course and short survival, similar to patients of acute leukemia. This disease is typically widespread by the time it is diagnosed, and is considered incurable using conventional chemotherapeutic approaches. However, as researchers are developing a better understanding of the underlying pathogenesis of the disease, and as novel agents and targets are emerging, some believe that clinical and molecular remission in younger patients of MCL is now within reach.

Treatment of MCL depends on the stage of the disease, the age of the patient, and the patient's overall health. Traditionally, first-line treatment for MCL is intensive induction chemotherapy coupled with autologous stem cell transplantation (ASCT). However, recent evidence suggests that allogeneic stem cell transplantation (allo-SCT) is better used to treat patients in relapse, while ASCT is better used to treat patients in initial therapy. Other studies have investigated whether ASCT in MCL patients is more effective when used in combination with total-body irradiation (TBI). However, results demonstrate that TBI modifies neither progression-free survival (PFS) nor overall survival (OS), and MCL transplant patients remain highly likely to relapse.

Learning Objectives

Upon completion of the Part II (*Transplant and Non-Transplant Therapies for Mantle Cell Lymphoma and Peripheral T-Cell Lymphoma*), participants should be able to:

- Analyze new data on non-transplant therapies for mantle cell lymphoma
- Compare the roles of transplant as initial therapy and transplant as salvage therapy for lymphomas
- Evaluate the data on autologous vs. allogeneic stem cell transplantations

Target Audience

The program will be oriented to a targeted audience of physicians and medical care professionals specializing in hematology, oncology, hematology, and blood and marrow transplantation.

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Faculty Disclosure

Consistent with the current Accreditation Council for Continuing Medical Education policy, the CME Provider must be able to show that everyone who is in a position to control the content of an individual educational activity has disclosed all relevant financial relationships. The CME Provider has a mechanism in place to identify and resolve any conflicts of interest discovered in the disclosure process. The presenting faculty members have all made the proper disclosures, and the following relationships are relevant:

John R. Wingard, MD, has no relevant financial relationships to disclose.

Jack W. Hsu has no relevant financial relationships to disclose.

Jan S. Moreb has no relevant financial relationshps to disclose.

Ginna G. Laport, MD, has no relevant financial relationships to disclose.

Sonali Smith, MD, has received honoraria from and been a consultant or speaker for Seattle Genetics, Celgene, and Onyx.

Introduction: Transplant and Non-Transplant Therapies for Mantle Cell Lymphoma and Peripheral T-Cell Lymphoma

Ginna G. Laport, MD

Non-Hodgkin lymphoma (NHL) is a complex group of 40 distinct entities. Despite this complexity, however, only histologic 6 subtypes account for approximately 75% of all cases of NHL. Diffuse large cell lymphoma (DLCL) is the most common, accounting for 31% of cases. Follicular lymphoma is the second most common subtype and comprises 22% of NHL cases. The next 3 most common subtypes—small lymphocytic lymphoma (SLL), mantle cell lymphoma (MCL), and peripheral T-cell lymphoma (PTCL)—together comprise only 6% of cases, and the remaining subtypes represent only 1% of cases.

Mantle Cell Lymphoma

MCL is characterized by a moderately aggressive clinical course. The median age at diagnosis is 63 years, and approximately 74% of cases occur in men. Although some investigators may use endoscopy or positron emission tomography (PET) scanning to assess the extent of disease at diagnosis, findings from these tests rarely result in upstaging or a change in therapy. In the vast majority of cases (> 90%), MCL has already progressed to advanced-stage disease at the time of diagnosis. Common sites of extranodal involvement include the bone marrow, blood, liver, and gastrointestinal tract. Molecular and chromosomal analysis also reveals the heterogeneity of MCL, which spans several immunophenotypes (CD20+, CD5+, CD23–, CCND1+, FMC7+, and bcl-1+) and common karyotypes, including t(11;14) and (q13;q32).

In 2008, investigators from the German Low Grade Lymphoma Study Group (GLSG) and European Mantle Cell Lymphoma Network developed the Mantle Cell International Prognostic Index (MIPI) to facilitate risk-assessment in patients with MCL [45]. The MIPI uses 4 independent predictors of survival in MCL—age, performance status, baseline LDH level, and leukocyte count—to classify patients as low, intermediate, or high risk. In the MIPI validation cohort, the low, intermediate, and high risk classifications corresponded with median overall survival times that were not yet reached, 51 months, and 29 months, respectively. In clinical practice, the MIPI can be used to develop risk-adapted treatment plans for patients with MCL.

Following the development of the MIPI, another key prognostic factor was identified in patients with MCL. The Ki-67 index is a measure of the percentage of Ki-67-positive cells in a lymph node biopsy specimen [46]. In a study of patients with MCL, the 3 risk groups defined by Ki-67 < 10%, 10% to < 30%, and ≥ 30% correlated with significantly different overall survival in patients treated with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) (P = .001) and in those treated with rituximab plus CHOP (R-CHOP) (P = .0126). The composite MIPI-Biologic (MIPI-B) risk-assessment tool accounts for both clinical and biologic prognostic factors in patients with MCL.

Peripheral T-Cell Lymphoma

PTCL is a heterogenous class of aggressive malignancies that accounts for approximately 10% to 15% of all cases of NHL. Significant geographic variations in the incidence and distribution of PTCL subtypes have been documented. In the Western hemisphere, PTCL occurs with low incidence (< 2%) and appears more commonly as nodal variants, including the PTCL-unspecified (PTCL-U) and anaplastic large-cell lymphoma (ALCL) subtypes. The incidence of PTCL increases to 18% in Asia, where extranodal subtypes are more common (Table 1).

PTCL affects primarily middle aged and elderly patients, and its clinical course is characterized by systemic symptoms, generalized lymphadenopathy, and blood and bone marrow involvement. Prognosis is poor for most patients with PTCL, with a 5-year survival rate of < 30%. Historically, the most commonly used risk-assessment tool in PTCL has been the International Prognostic Index (IPI), which was developed in 1993 to evaluate patients with aggressive NHL [47]. The IPI incorporates information on 5 patient characteristics: patient age, serum LDH, performance status, disease stage, and nodal status. The relative risk of death can be estimated according to the number of factors present at diagnosis: 0 or 1 (low), 2 (low/intermediate), 3 (high/intermediate), or 4 or 5 (high).

In 2004, investigators from the Italian Lymphoma Intergroup revised the IPI in an effort to make it more applicable to patients with PTCL [48]. Their result, the Prognostic Index for PTCL (PIT), incorporates just 4 risk factors: age ≥ 60 years; ECOG performance status ≥ 2, elevated LDH, and bone marrow involvement. The PIT prognostic model identifies 4 risk groups based on the number of risk factors present at diagnosis: 0 (Group 1), 1 (Group 2), 2 (Group 3), 3 or 4 (Group 4). In the validation cohort, the 5-year overall survival rates for patients with MCL in Groups 1, 2, 3, and 4 were 62%, 53%, 33%, and 18%, respectively.

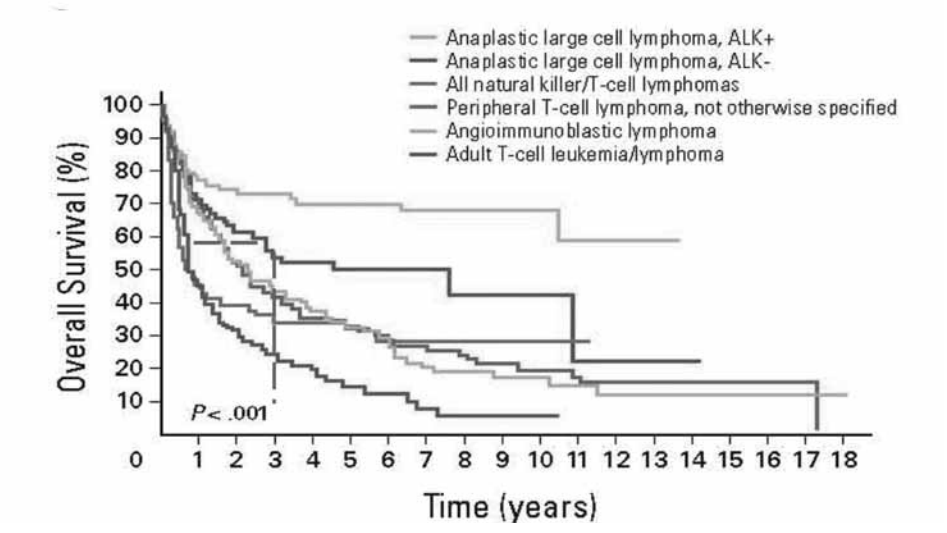

Figure 1. Poor survival outcomes for most subtypes of peripheral T-cell lymphoma [50].

Table 1. World Health Organization (WHO) Classification System for Peripheral T-Cell Lymphomas [49]*

Predominantly Nodal	**Predominantly Extranodal**
· Peripheral T-cell lymphoma, not otherwise specified	· Natural killer/T-cell lymphoma, nasal/type
· Angioimmunoblastic T-cell lymphoma	· Enteropathay-associated T-cell lymphoma
· Anaplastic large cell lymphoma, ALK-positive	· Hepatosplenic T-cell lymphoma
· Anaplastic large cell lymphoma, ALK-negative	· Epstein-Barr virus–associated T-cell lymphoproliferative disorder of childhood
Predominantly Leukemic	**Predominantly Cutaneous**
· T-cell prolymphocytic leukemia	· Mycosis Fungoides
· T-cell large granular lymphocyte leukemia	· Primary cutaneous CD30+ T-cell lymphoproliferative disorder
· Chronic lymphoproliferative disorder of natural killer cells	· Primary cutaneous peripheral T-cell lymphoma
· Aggressive natural killer cell leukemia	· Sezary syndrome
· Adult T-cell leukemia/lymphoma	· Subcutaneous panniculitis-like T-cell lymphoma
	· Primary cutaneous CD8+ cytotoxic T-cell lymphoma
	· Primary cutaneous small/medium CF4+ T-cell lymphoma

*ALK indicates anaplastic lymphoma kinase.

PTCL Subtypes

In 2008, the World Health Organization published an updated classification system for PTCL [49]. The new classification system recognizes 20 PTCL subtypes, which are described as predominantly nodal, predominately extranodal, predominantly leukemic, and predominantly cutaneous (Table 1).

Investigators from the International T-Cell Lymphoma Project examined tissue biopsies, immunophenotypic markers, genetic studies, and clinical data from 1,314 patients diagnosed with PTCL or natural killer/T-cell lymphoma (NK T-Cell) from 22 centers worldwide to determine the relative frequencies and geographic variations of histologic subtypes [50]. The most common subtypes were PTCL-not otherwise specified (PTCL-NOS), also known as PTCL-U (25.9%), angioimmunoblastic type (18.5%), NK T-Cell (10.4%), adult T-cell leukemia/lymphoma (ATLL; 9.6%), anaplastic lymphoma kinase (ALK)-positive ALCL (6.6%), and ALK-negative ALCL (5.5%).

With standard therapy, survival outcomes varied significantly across the PTCL subtypes (Figure 1). Patients with ALK-positive ALCL had the most favorable prognosis, with a 5-year overall survival rate of 70%. By comparison, the 5-year survival rate was 32% for patients with the PTCL-U, angioimmunoblastic, and NK T-Cell subtypes, and 14% and for patients with ATLL ($P < .001$). Several transplantation and non-transplantation strategies are currently under evaluation in the frontline and relapse/refractory settings to improve outcomes in patients with PTCL.

Non-Transplant Treatment Options for Mantle Cell Lymphoma and T-Cell Lymphoma

Sonali Smith, MD

Although MCL and T-cell lymphoma arise from separate cell lineages, these malignancies share common features related to clinical management. For instance, in both cases, newly diagnosed disease is treated with some form of induction regimen, most commonly chemotherapy. Both cancers are associated with a poor prognosis that warrants consideration of consolidation therapy, often involving autologous or, rarely, allogeneic transplantation. Maintenance therapy can be used in MCL, whereas this approach is till being explored in T-cell lymphoma to prolong the duration of remission. The risk of relapse is high in both tumor types, and after relapse, transplantation is often considered. Finally, several novel agents are being developed to expand treatment options for relapsed/refractory disease.

Mantle Cell Lymphoma

Estimates suggest that 10-15% of patients with MCL will have an indolent presentation with no acute indication for treatment. For these patients, a "watch and wait" approach is an appropriate management strategy. The majority of patients with MCL, however, have a classic presentation. Historically, treatment options for newly diagnosed MCL could be classified as intensive regimens, which were typically reserved for younger patients, and less-intensive strategies, which were preferred for older patients and those with comorbidities or other contraindications to aggressive therapy. Intensive frontline therapies typically included an alkylating agent or cytarabine and incorporated autologous HTC for patients who responded to high-dose therapy. By comparison, less intensive strategies for newly diagnosed MCL have incorporated agents such as alkylating agents, purine analogs, or bendamustine or involved the palliative use of steroids or single-agent rituximab.

Treatment approaches for newly diagnosed MCL are evolving away from this strict framework of intensive versus less-intensive therapy. Based on recent clinical trial evidence, many patients who meet the classic criteria for intensive therapy are now being treated with non-transplantation approaches.

R-CHOP-Based Induction Therapy

Several clinical trials have firmly established the role of immunochemotherapy with CHOP (R-CHOP) as one treatment backbone for patients with previously untreated MCL [51-53]. The German Low Grade Lymphoma Study Group (GLSG) compared CHOP (n = 60) and R-CHOP (n = 62) in patients with previously untreated advanced-stage MCL [51]. Patients up to age 65 years who achieved PR or CR underwent a second randomization to myeloablative analogous HCT or interferon alfa (IFN-alpha) maintenance, while all patients older than 65 years were treated with IFN-alpha maintenance. R-CHOP was superior to CHOP in terms of overall response rate (94% versus 75%; $P = .0054$), CR rate (34% versus 7%; $P = .00024$), and median time to treatment failure (21 months versus 14 months; $P = .0131$). Treatment toxicity was acceptable, with no major differences between R-CHOP and CHOP.

In 2011, Ruan and colleagues evaluated the addition of dose-escalated bortezomib to R-CHOP in patients with previously untreated MCL (n = 36) or diffuse large B-cell lymphoma (DLBCL) (n = 40) [52]. Patients received standard R-CHOP therapy every 21 days plus bortezomib 0.7, 1.0, or 1.3 mg/m^2 on days 1 and 4 for 6 cycles. The median age was 63 years (range, 20 to 87 years), and prognosis was generally unfavorable, with MCLIPI scores indicating intermediate-risk disease in 28% and high-risk disease in 39%. Among evaluable patients with MCL, the overall response rate was 91%, including 72% of patients with CR or CR-unconfirmed (CRu). In the intent-to-treat analysis, the 2-year progression-free survival was 44%, and the 2-year overall survival was 86%. Bortezomib, therefore, can be safely added to standard R-CHOP therapy to enhance frontline treatment outcomes in MCL.

The ECOG E1499 study evaluated the use of consolidation therapy with yttrium-90 (^{90}Y)-ibritumomab tiuxetan after brief frontline therapy with 4 cycles of R-CHOP in 56 patients with previously untreated MCL [53]. The median patient age was 60 years. The overall response rate was 82%, including a CR/CRu in 55% of patients. The median time to treatment failure was 34.2 months, and the estimated 5-year overall survival was 73%. There were no unexpected toxicities associated with treatment. Thus, the regimen of 4 cycles of R-CHOP followed by ^{90}Y-ibritumomab tiuxetan consolidation therapy compared favorably with historical results with 6 cycles of R-CHOP as frontline therapy for MCL.

Rituximab Maintenance Therapy

Most studies of R-CHOP in newly diagnosed MCL show a very high overall response rate, but a short duration of response [51-53]. The natural history of MCL indicates that relapse is almost inevitable. Therefore, another emerging area of research in MCL focuses on strategies to prolong the response to frontline treatment and delay disease progression.

In 2012, the European MCL Network reported findings from a prospective trial in 560 older patients (median age, 70 years) with newly diagnosed MCL [54]. The trial included 2 randomization schemes. First, the trial randomly assigned patients to induction therapy with fludarabine, cyclophosphamide, and rituximab (R-FC) versus R-CHOP. Second, patients who responded to induction therapy were randomly assigned to maintenance therapy with rituximab versus IFN-alpha. Results from the first randomization showed significantly worse 4-year overall survival with R-FC compared with R-CHOP (47% versus 62%; P = .005). Therefore, R-FC will not be further evaluated as an induction regimen for patients with newly diagnosed MCL.

Results from the second randomization showed a significant advantage with rituximab maintenance with a median follow-up of 36 months (Figure 1). In the overall study population, the median duration of response was 75 months with rituximab maintenance, compared with 27 months with IFN-alpha (P < .001). Among the subgroup of patients who received R-CHOP induction therapy, the median duration of response was not met in the rituximab maintenance group, compared with 23 months in the IFN-alpha group (P < .001).

Induction Therapy with Bendamustine-Rituximab

Another strategy for improving response duration involves more effective induction therapy. The phase III Study Group Indolent Lymphomas (StiL) trial showed a dramatic improvement in progression-free survival with first-line bendamustine plus rituximab (B-R) compared with standard R-CHOP induction therapy in patients with indolent B-cell lymphoma and transplantation-ineligible MCL [55]. The prospective, multicenter, randomized, open-label, non-inferiority StiL trial enrolled 546 patients with previously untreated stage III or IV indolent or mantle-cell lymphoma and randomly assigned patients to treatment with B-R (n = 274) or R-CHOP (n = 275). Patients in the B-R group received bendamustine 90 mg/m^2 on days 1 and 2 and rituximab 375 mg/m^2 on day 1 of each 4-week cycle for a maximum of 6 cycles. Patients in the R-CHOP study arm received the standard CHOP regimen every 3 weeks plus rituximab 375 mg/m^2 on day 1 of each cycle for a maximum of 6 cycles. The primary endpoint was progression-free survival.

At the 2012 American Society of Clinical Oncology (ASCO) annual meeting, Rummel and colleagues reported updated results from the StiL trial, and full results were published in The Lancet in 2013 [55,56]. After a

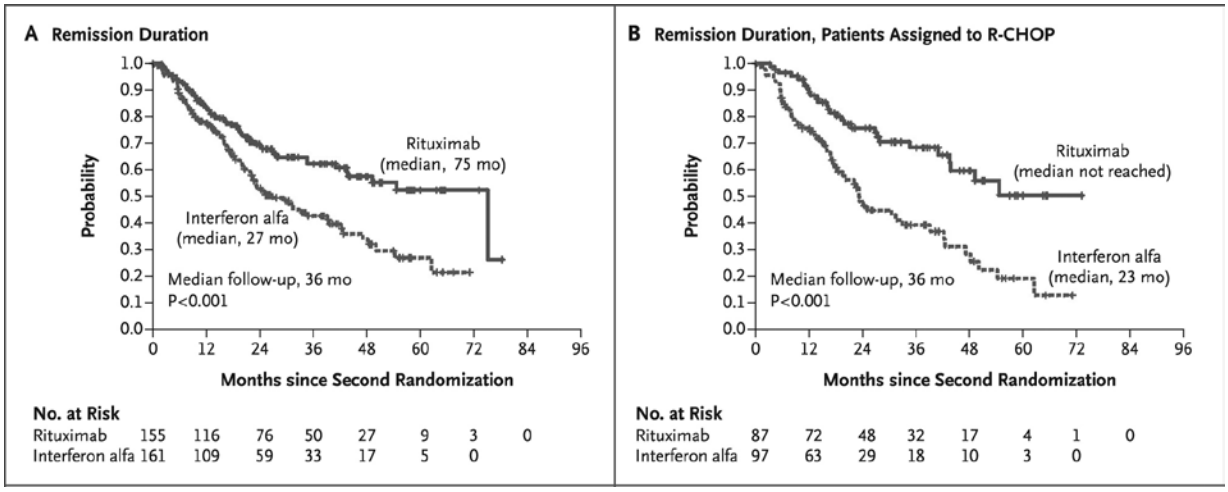

Figure 1. Maintenance rituximab in patients with newly diagnosed mantle cell lymphoma [54]. R-CHOP indicates cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) and rituximab.

median follow-up of 45 months, the median progression-free survival was 69.5 months in the B-R group, compared with 31.2 months in the R-CHOP group (HR, 0.58; $P < .0001$). The superiority of B-R was consistent for all histological subtypes, except marginal zone lymphoma. Among patients with MCL (n = 93), the median progression-free survival was 35.4 months with B-R and 22.1 months with R-CHOP (HR, 0.49; $P = .0044$). Overall survival did not differ between the treatment groups. Additional follow-up may reveal differences in long-term survival outcomes.

Induction therapy with B-R was also better tolerated than R-CHOP, with a lower rate of hematologic toxicity (30% versus 68%; $P < .0001$), infection (37% versus 57%; $P = .0025$), peripheral neuropathy (7% versus 29%; $P < .0001$), and stomatitis (6% versus 19%; $P < .0001$), and a lower rate of alopecia after ≥ 3 cycles (0% versus 100%; $P < .0001$). The only adverse event to occur more commonly in the B-R arm compared with R-CHOP was erythematous skin reactions (16% versus 9%; $P = .024$). Thus, results from the phase III StiL trial support the preferred use of B-R as first-line treatment of indolent lymphoma compared with R-CHOP, due to increased progression-free survival and fewer short-term toxic effects.

The phase III BRIGHT trial also evaluated the safety and efficacy of induction therapy with B-R compared with the standard induction regimens of R-CHOP and rituximab, cyclophosphamide, vincristine, and prednisone (R-CVP) in patients with indolent NHL or MCL [57]. Patients were randomly assigned to receive either B-R (n = 221) or the investigator's choice of R-CHOP or R-CVP (n = 215). The B-R regimen consisted of bendamustine 90 mg/m^2 on days 1 and 2 plus rituximab 375 mg/m^2 on day 1 of each 28-day cycle for 6 to 8 cycles. The R-CHOP and R-CVP arms used standard dosing and 21-day cycles. The primary endpoint was non-inferiority of CR rate.

The BRIGHT trial met the primary endpoint and showed that the CR rate with B-R was non-inferior to that of standard induction therapy with R-CHOP or R-CVP. The CR rate in the B-R and R-CHOP/R-CVP groups, respectively, was 31% and 25% for all evaluable patients (HR, 1.25; $P = .0225$) and 31% and 23% for all randomized patients (HR, 1.34; $P = .0084$). Because the non-inferiority endpoint was met, investigators also tested for superiority. In the subgroup of patients with MCL, treatment with B-R was associated with a significantly higher CR rate compared with R-CHOP/R-CVP (51% versus 24%; $P = .0180$ for superiority). Time-to-event data are immature in this study population, and additional follow-up is required to determine whether improved CR rates translate to prolonged progression-free and overall survival.

Emerging Agents in Relapsed/Refractory MCL

Advances in gene expression and molecular profiling have revealed the importance of B-cell receptor (BCR) signaling pathways in the survival of normal and malignant B-cells [58]. Many of the kinases involved in BCR are now being investigated as potential therapeutic targets for B-cell malignancies, including MCL (Table 1).

Idelilisib (CAL-101, GS1101) is an investigational agent that targets the class I phosphatidylinositol 3-kinases (PI3Ks) to disrupt BCR signaling. Expression of the PI3K p110δ isoform (PI3Kδ) is exclusive to cells of hematopoietic origin, and constitutive activation of the PI3Kδ-dependent PI3K pathway has been observed in NHL cells. Idelilisib is an oral PI3K inhibitor that selectively inhibits the PI3Kδ isoform to induce apoptosis in NHL cells. In a phase I study, idelilisib showed promising clinical activity in patients with relapsed or refractory indolent NHL and MCL [62]. In the subgroup of patients with MCL, 16 of 21 patients (76%) exhibited tumor shrinkage in response to idelilisib. The high rate of tumor response and prolonged duration of tumor control observed with idelilisib in heavily pretreated patients with indolent NHL or MCL warrants further study, both as single-agent oral therapy and in combination with other chemotherapy and/or immunotherapy regimens.

Ibrutinib is another investigational agent that shows promise in MCL. Ibrutinib acts by inhibiting Bruton's tyrosine kinase (BTK), another key mediator of B-cell receptor signaling. At the 2012 ASH annual meeting, (and now published in *The New England Journal of Medicine 2013*), Wang and colleagues presented findings from an international phase II trial of ibrutinib in 115 patients with relapsed or refractory MCL [63]. All patients received oral ibrutinib 560 mg daily in continuous 28-day cycles until disease progression. Evaluable patients were classified as either bortezomib-naïve (n = 63) or bortezomib-exposed, with at least 2 prior cycles of bortezomib (n = 47).

The overall response rate among all patients was 68%, including a CR rate of 22%. Overall response rates were similar in the bortezomib-naïve (65%) and bortezomib-exposed (72%), with a similar proportion of CRs (21% and 23%, respectively). After a median follow-up of 9.1 months, the median duration of response was not reached. The median progression-free survival was 13.9 months. Based on these findings, a clinical trial of ibrutinib in patients with relapsed or refractory MCL following treatment with bortezomib is currently underway.

T-Cell Lymphoma

With the exception of ALK-positive anaplastic large-cell lymphoma, the prognosis for most subtypes of PTCL is very poor. CHOP-based therapies are the most commonly prescribed first-line regimens, but the cure rate with standard CHOP is low, resulting in a 5-year survival rate of less that 30% for most histologic subtypes. Given the poor outcomes associated with current therapy, the National Comprehensive Cancer Network recommends

Table 1. Emerging Agents in Relapsed and Refractory Mantle Cell Lymphoma*

Agent	Class	Overall Response Rate	Other Outcomes
Bortezomib [59,60]	Proteasome inhibitor	30% to 50%	Median PFS: 6 to 12 months
Lenalidomide [61]	Immunomodulatory agent	57%	Median DR: 18+ months
Idelilisib [62]	PI3K inhibitor	48%	NR
Ibrutinib [63]	BCR-signaling inhibitor	68%	Median PFS: 13.9 months

*PFS indicates progression-free survival; DR, duration response; PI3K, phosphatidylinositol 3-kinase p110 isoform; NR, not reported; BCR, B-cell receptor.

enrollment in clinical trials for patients with previously untreated PTCL [64].

Building on First-Line CHOP Therapy

Chemotherapy with CHOP-based regimens comprises the backbone of most front-line therapies for PTCL. Several studies, however, illustrate the limitations of this approach. Agents such as etoposide, alemtuzumab, denileukin diftitox, and bortezomib have also been evaluated in combination with CHOP in patients with previously untreated PTCL.

In 2004, Savage and colleagues described outcomes in 199 patients with PTCL who were treated at the British Columbia Cancer Agency [65]. Treatment varied by PTCL subtype, but the majority of patients (71% to 90%) received CHOP-based chemotherapy. The IPI score was able to predict a difference in survival between 2 major subgroups defined as low risk (IPI 0 or 1) and poor risk (IPI ≥ 2). For patients with the most common histologic subtype, PTCL-U (n = 117), the 5-year overall survival was 20% in the poor-risk group and 64% in the low-risk group (P < .00001). Overall, findings from this single-institution analysis demonstrate that treatment with standard CHOP-based chemotherapy is ineffective for most patients with PTCL.

More recently, investigators from the German High-Grade Non-Hodgkin Lymphoma Study Group (DSHNHL) conducted a pooled analysis of 289 patients with T-cell lymphoma who were treated with CHOP or CHOP plus etoposide (CHOEP) while enrolled in prospective phase II or phase III studies of the DSHNHL [67]. The 4 most common histologic subtypes were ALK-positive ALCL (n = 78), ALK-negative ALCL (n = 113), PTCL-U (n = 70), and angioimmunoblastic T-cell lymphoma (AITL; n = 28). Patients with ALK-positive ALCL had the most favorable outcomes, including a 3-year event-free survival rate of 76%, and a 3-year overall survival rate of 90%. Outcomes for all other subtypes were poor, with 3-year event-free survival rates ranging from 41% to 50%, and 3-year overall survival rates ranging from 54% to 68%. The addition of etoposide improved the 3-year event-free survival rate compared with standard CHOP (75% versus 51%; P = .003), but only in the subgroup of patients aged 60 years or younger with normal baseline LDH levels.

Alemtuzumab, a monoclonal antibody that selectively targets the CD52 cell-surface antigen that appears on T-cells and B-cells, has also been added to standard first-line CHOP chemotherapy for patients with PTCL [68-70]. In these trials, overall response rates following treatment with alemtuzumab-CHOP ranged from 75% to 90%, with CR rates of 60% to 71% [68-70]. Treatment is also associated with a high risk of infectious and hematologic complications, including febrile neutropenia, posttransplantation lymphoproliferative disease (PTLD), cytomegalovirus (CMV) reactivation, and secondary Epstein-Barr virus (EBV)-related lymphoma. Therefore, although the alemtuzumab-CHOP combination induces high response rates, treatment requires close monitoring and post-treatment surveillance.

Novel Therapies in PTCL

Treatment options for PTCL are expanding with the approval of new agents and the development of novel therapies and combination regimens. Some of the many therapeutic classes evaluated in PTLC include chemotherapeutic agents, such as bendamustine, gemcitabine, and pralatrexate; histone deacetylase (HDAC) inhibitors, including romidepsin and belinostat; monoclonal antibodies and antibody-drug conjugates such as brentuximab vedotin and zanolimumab; and other agents such as lenalidomide and novel Aurora A kinase inhibitors. Recent data evaluating the safety and efficacy of just a few of these agents are summarized below.

Pralatrexate

Pralatrexate is a new intravenous antifolate drug designed to accumulate preferentially in tumor cells as a result of its high affinity for reduced folate carrier type 1 (RFC-1), a protein that is overexpressed on cancer cells [71]. Pralatrexate is also the first agent to gain FDA approval for the treatment of patients with relapsed or refractory PTCL.

Pralatrexate was approved for the treatment of relapsed or refractory PTCL on the basis of findings from the phase II PROPEL study [72]. The prospective trial enrolled 115 patients who had a median of 3 prior systemic therapies (range, 1 to 12). Patients were treated with IV pralatrexate 30 mg/m^2 weekly for 6 weeks in 7-week cycles. In 109 evaluable patients, the overall response rate was 29%, including 12 patients who achieved a CR (11%) and 20 patients with a PR (18%). The responses were durable, with a median duration of response of 10.1 months. Responses were also consistent across patient subgroups defined by age, histologic subtype (with the exception of AITL, which showed poor response), amount of prior therapy, prior exposure to methotrexate, and prior autologous HTC. The median progression-free survival was 3.5 months, and the median overall survival was 14.5 months.

In the PROPEL trial, the most common grade 3-4 adverse events were thrombocytopenia (32%), mucositis (22%), neutropenia (22%), and anemia (18%) [72]. Supplementation with vitamin B12 and folic acid can prevent some drug-related toxicities associated with pralatrexate.

Based on the activity of pralatrexate therapy in relapsed and refractory PTLC, there is interest in moving this agent to the front-line setting. A phase II study of pralatrexate in combination with cyclophosphamide, etoposide, vincristine, and prednisone (CEOP) in patients with previously untreated PTCL is current underway (NCT01336933). The investigator-initiated trial completed enrollment with 34 patients with stage II-IV PTCL in January 2013.

Romidepsin

Romidepsin is a HDAC inhibitor that was discovered to show activity against peripheral and cutaneous T-cell lymphoma in 2001 [73]. Romidepsin gained FDA approved in 2009 for the treatment of CTCL in patients who received at least 1 prior systemic therapy. In 2011, the romidepsin indication was expanded to include treatment for PTCL in patients who have received at least 1 prior therapy. The FDA granted romidepsin fast-track status for PTCL based on its potential to address a significant unmet medical need for patients. Romidepsin has also been granted orphan-drug status in the United States and European Union in PTCL.

The PTCL approval was based on the results of 2 phase II studies of patients with PTCL who had failed prior therapy [74,75]. At the ASH 2011 annual meeting, Coiffier and colleagues presented the final results of an international, multicenter, open-label, phase II study of 130 patients with PTCL [74]. Patients had failed a median of 2 prior systemic therapies (range, 1 to 8), and 16% had failed prior HTC. All patients received IV romidepsin 14 mg/m^2 over 4 hours on days 1, 8, and 15 every 28 days for a maximum of 6 cycles. As assessed by an independent review committee, the overall response rate was 25%,

including CR/CRu in 15% of patients. Another 25% of patients had stable disease, and 49% had progressive disease or were not evaluable. Responses to romidepsin were durable. The median duration of response was 17 months for all responders, as well as for those who achieved a CR/CRu. The median time to any response was 2 months, and the median time to CR/CRu was 4 months. The median time to progression was 6 months.

Piekarz and colleagues reported findings from the second phase II trial of romidepsin in patients with previously treated PTCL [75]. The multicenter trial enrolled 47 patients with PTCL who had received a median of 3 prior treatments (range, 1 to 11), including HTC in 18 patients (38%). The overall response rate was 38%, including a CR in 8 patients (18%). The median duration of response was 8.9 months for all responses (range, 2 to 74 months), and 30 months for patients who had achieved a CR (range, 3 to 73). These findings also support the use of single-agent romidepsin to induce durable responses in patients with relapsed PTCL.

Bendamustine

Bendamustine is an alkylating agent with antimetabolite activity that is currently approved for the treatment of CLL and the treatment of indolent B-cell NHL that has progressed during or within 6 months of treatment with rituximab or a rituximab-containing regimen. Based on the activity of bendamustine in CLL and indolent B-cell NHL, there is interest in the potential role of this agent in the treatment of T-cell lymphomas.

The prospective, multicenter, open-label, phase II BENTLY trial evaluated bendamustine in 60 patients with PTCL (n = 58) or CTCL (n = 2) who progressed after 1 or more prior lines of chemotherapy [76]. All patients received bendamustine 120 mg/m^2 on day 1 and 2 of every 3 weeks for 6 cycles. The bendamustine dose was reduced to 90 mg/m^2 in patients who developed any grade 4 hematologic toxicities or any grade ≥ 3 non-hematologic adverse event. A second dose reduction to 60 mg/m^2 was permitted to avoid further treatment delay. The most frequent ≥ 3 adverse events were neutropenia (30%), thrombocytopenia (24%), and infections (20%).

After 3 cycles, the overall response rate was 50%, including CR/CRu in 17 patients (28%) and PR in 13 patients (22%). The high response rate was consistent across major PTCL subtypes, independent of patient age or treatment history. The median duration of response was 3.5 months (range, 1 to 20.7 months). The median progression-free survival was 3.6 months, and the median overall survival was 6.2 months.

Brentuximab

Brentuximab (SGN-35) is an investigational anti-drug conjugate that includes a CD30-targeted antibody conjugated to monomethylauristatin E (MMAE), an anti-tubulin agent. Preclinical data show that brentuximab selectively induces apoptosis in CD30-positive HL and ALCL tumor cells by binding to the CD30 cell-surface antigen, becoming internalized, and releasing MMAE within the malignant cells [77].

In 2012, Pro and colleagues reported results of a phase II multicenter trial of brentuximab in patients with relapsed or refractory systemic ALCL [78,79]. The trial included 58 patients with a median age of 52 years (range, 14 to 76 years) with a diagnosis of ALK-positive (28%) or ALK-negative (72%) ALCL. Patients had been treated with a median of 2 previous chemotherapy regimens (range, 1 to 6), and 50% of patients were refractory to their last regimen. All patients were treated with IV brentuximab 1.8 mg/kg every 3 weeks, delivered over 30 minutes as an outpatient infusion.

The objective response rate was 86%, including CR in 57% of patients and PR in 29% of patients. Responses were durable, with a median of 12.6 months for any response and 13.2 months for a CR. The median progression-free survival was 13.3 months. The most common grade ≥ 3 adverse events were neutropenia (21%), thrombocytopenia (14%), and peripheral neuropathy (12%).

Summary

For transplantation ineligible patients with previously untreated MCL, current non-transplantation modalities are highly effective. The use of maintenance therapy can prolong the duration of remission. New agents and combinations are being tested for patients with relapsed and refractory MCL, and many of these regimens may move up to the frontline setting. The treatment of PTCL is more challenging. With current CHOP-based regimens in the frontline setting, outcomes remain poor for most patients. New agents are under evaluation for the treatment of PTCL, with the goal of improving response and prolonging the duration of remission.

Hematopoietic Cell Transplantation: Mantle Cell Lymphoma and Peripheral T-Cell Lymphoma

Ginna G. Laport, MD

Hematopoietic Cell Transplantation in MCL

The treatment of MCL has evolved from conventional CHOP-based chemotherapy to more intensive regimens that incorporate rituximab and high-dose cytarabine (Figure 1). Transplantation options have also expanded to include autologous HTC in the frontline and relapsed setting, as well as reduced-intensity allogeneic HTC for a wide population of patients, including older patients and those who are not candidates for myeloablative conditioning.

Autologous HTC for MCL

Data from the EBMT registry and Autologous Blood and Marrow Transplant Registry (ABMTR) illustrate early outcomes associated with autologous HTC in patients with MCL [80]. The registry analysis included 195 patients who received analogous HCT for MCL between 1988 and 1998 and followed for a median of 3.9 years. In this cohort, overall survival was 76% at 2 years and 50% at 5 years. Progression-free survival at 2 years and 5 years were 55% and 33%, respectively. The survival findings highlighted the importance of transplantation performed during first CR. For patients with chemosensitive disease but not in first CR, the hazard ratio for death was 2.99 (P < .001) compared with patients who received transplants in first CR.

The Nordic Lymphoma Group conducted 2 phase II trials that established the role of first-line, dose-intense analogous HCT for patients with MCL. In the first trial, MCL-1, 41 patients received 4 cycles of CHOP-based chemotherapy ("maxi-CHOP") followed by carmustine, etoposide, cytarabine, melphalan (BEAM) and peripheral blood stem cell transplantation [81].

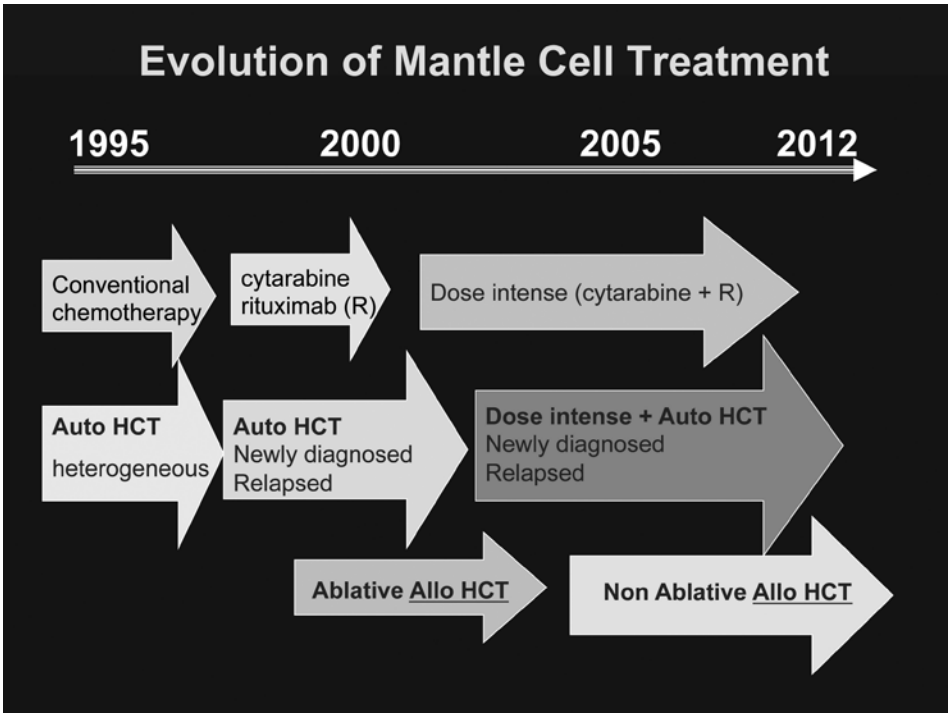

Figure 1. Evolution of treatment for mantle cell lymphoma. Allo indicates allogeneic; auto, autologous; HCT, hematopoietic cell transplantation.

The goal of the second Nordic Lymphoma Group trial, MCL-2, was to increase remission and survival rates compared with MCL-1. In MCL-2, 160 patients received 6 cycles of dose-intensive induction immunochemotherapy with rituximab plus alternating cycles of maxi-CHOP and high-dose cytarabine, also followed by analogous HCT [82,83]. Rituximab consolidation was used in patients with presumptive relapse, based on molecular monitoring of blood and bone marrow by real-time PCR. Patients received in vivo rituximab-purged stem cell support with BEAM or carmustine, etoposide, cytarabine, cyclophosphamide (BEAC) to reduce the risk of contamination of MCL cells in the stem cell pool.

In a comparison of trial outcomes, the MCL-2 treatment regimen was associated with significant improvements in response, remission, and survival [82,83]. The overall response rate was significantly higher following treatment with the MCL-2 induction regimen compared with MCL-1 (96% versus 76%, respectively; $P < .0005$), as was the rate of CR/CRu (54% versus 27%, respectively; $P < .001$). The 5-year event-free survival rate was 63% in the MCL-2 study, compared with 15% in MCL-1 ($P < .0001$). Overall survival at 5 years in the MCL-2 and MCL-1 cohorts were 75% and 41%, respectively ($P < .001$) [83].

In 2012, Geisler and colleagues reported long-term results from the Nordic MCL-2 trial [84]. With a median follow-up of 6.5 years, outcomes remained encouraging, with a median event-free survival of 7.4 years. Both the median overall survival and median response duration were longer than 10 years. The long-term findings confirmed the utility of MIPI risk group and Ki-67 expression, combined into the composite MIPI-Biological Index (MIPI-B), as a prognostic factor in MCL. More than 70% of patients classified as low-intermediate risk based on MIPI-B were alive at 10 years, compared with only 23% of patients classified as high-risk based on MIPI-B.

High-dose cytarabine has emerged as a key component of induction therapy and conditioning prior to analogous HCT in younger patients with MCL. At the 2012 ASH annual meeting, Hermine and colleagues from the European Mantle Cell Lymphoma Network presented results from the phase III MCL Younger Trial [85]. Findings from the trial demonstrated that 3 alternating courses of R-CHOP and rituximab plus dexamethasone, cytarabine, cisplatin (R-DHAP), compared with R-CHOP, increased clinical and molecular responses to induction therapy in patients with MCL. The MCL Network Trial enrolled 497 patients aged <65 years (median, 55 years) with previously untreated stage II-IV MCL. Patients were randomly assigned to induction therapy with 3 alternating courses of R-CHOP and R-DHAP followed by a myeloablative conditioning (10 Gy TBI, cytarabine 5 g/m^2, and melphalan 120 mg/m^2) and analogous HCT (n = 248) or 6 courses of R-CHOP followed by myeloablative radiochemotherapy (12 Gy TBI and cyclophosphamide 60 mg/kg 2) and analogous HCT (n = 249).

Treatment with the R-CHOP/R-DHAP induction regimen significantly prolonged the duration of remission compared with standard R-CHOP. The median duration of remission was not reached in the R-CHOP/R-DHAP group, compared with 55 months in the R-CHOP group ($P < .0001$). Median overall survival was not reached in either treatment arm, but the analysis showed a significant survival advantage in favor of the R-CHOP/R-DHAP regimen ($P = .048$). Importantly, the R-CHOP/R-DHAP was superior to R-CHOP in all MIPI risk groups.

Allogeneic HTC for MCL

An analysis of data from the CIBMTR shows trends in survival after transplant in MCL (Figure 2). Between 2000 and 2010, a total of 4,116 transplantations were performed in patients with MCL in the United States. The vast majority of these were autologous transplantations (n = 3,173), with only 554 HLA-matched sibling donor allogeneic transplantations and 389 unrelated donor allograft procedures during this time period. Survival curves show a significant advantage in favor of autologous transplantation, followed by sibling donor allografts ($P < .0001$). Unrelated donor allograft recipients had the poorest survival outcomes. It should be emphasized that this is registry data with a heterogeneous group of patients. The allogeneic group usually contains patients who are more heavily pre-treated, failed a prior autologous HCT or have higher risk disease.

Given the dearth of effective treatment options in the relapsed/refractory setting, reduced-intensity and/or nonmyeloablative allogeneic HTC is increasingly being considered for patients with relapsed or refractory MCL. Table 1 summarizes the range of recent international experiences with this treatment modality [86-89]. Despite a refractory disease state, many patients with MCL were able to attain durable remission after allogeneic HTC.

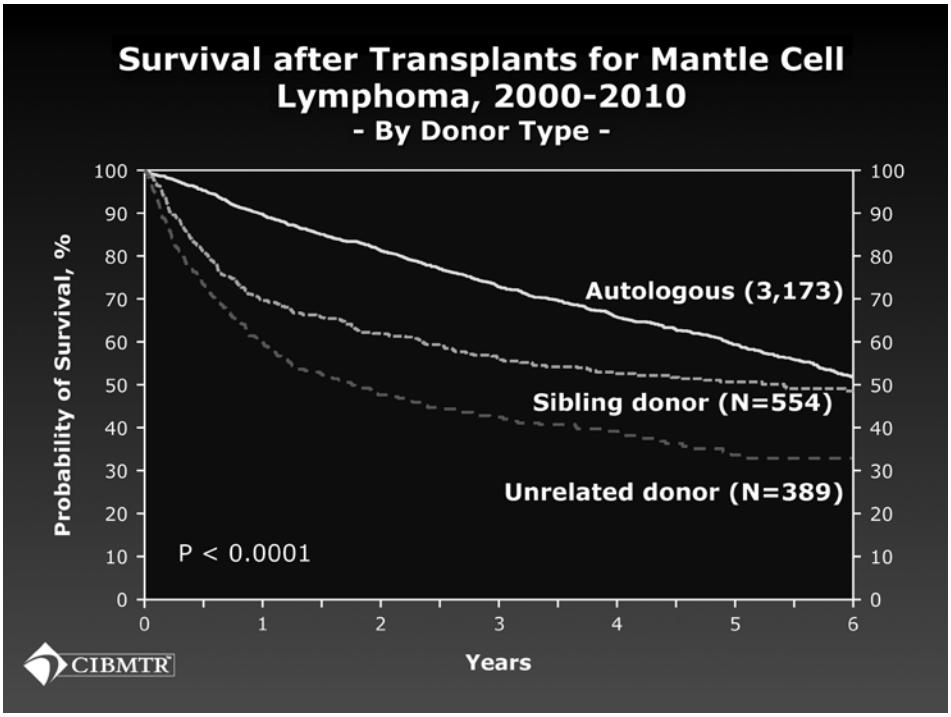

Figure 2. Survival after transplantation for mantle cell lymphoma, 2000 to 2010.

Two prognostic factors consistently predict more favorable event-free and overall survival outcomes following allogeneic HTC [86-89]. These include transplantation during first CR, suggesting the presence of chemosensitive disease, and less heavily pretreated disease, defined as exposure to less than 2 to 4 prior chemotherapy regimens. The presence of chemotherapy-unresponsive disease, however, should not preclude the use of allogeneic HTC. Indeed, in the CIBMTR registry study, the intensity of the conditioning regimen did not influence any efficacy outcomes following allogeneic HSCT [86]. Progression-free survival, overall survival, non-relapse mortality, or relapse duration were nearly equivalent among patients who received myeloablative conditioning (n = 74) and those who received reduced-intensity/nonmyeloablative conditioning (n = 128). Approximately 25% of all patients with chemotherapy-unresponsive MCL were able to achieve durable remission following allogeneic HTC, regardless of conditioning regimen.

Hematopoietic Cell Transplantation for PTCL

The optimal role of HTC for patients with PTCL has been difficult to define. Clinical trial evidence provides only limited insight, given the heterogeneity of PTCL and divergent findings across histologic subtypes.

Autologous HTC in Relapsed/Refractory PTCL

To improve the identification of appropriate candidates for transplantation, 2 recent single-institution studies explored the prognostic significance of various patient and disease characteristics in patients undergoing analogous HCT for PTLC. In 2011, Nademanee and colleagues described outcomes of high-dose therapy and analogous HCT in a retrospective study of 67 patients with PTLC who were treated at the City of Hope Medical Center in Duarte, California [90]. All patients had relapsed or primary refractory disease following initial induction chemotherapy for PTCL-U (n = 30), ALCL (n = 30), or AITL (n = 7). The median patient age was 48 years. Patients younger than age 60 were treated with 1200 cGy TBI followed by etoposide 60 mg/kg and cyclophosphamide 100 mg/kg prior to analogous HCT. For patients aged 60 years or older, or for those with prior exposure to radiation therapy, the conditioning regimen consisted of carmustine 450 mg/m2 or standard-dose BEAM in place of TBI. The median follow-up was 5.5 years.

For all patients, the 5-year overall survival was 54%, and the 5-year progression-free survival was 40%. However, outcomes differed significantly according to disease status at the time of transplantation. The 5-year progression-free survival was 75% for patients who underwent transplantation during first complete or partial remission, compared with 32% for patients who underwent transplantation with relapsed or induction-failure disease (P = .0138). The PIT score at transplantation also correlated with survival. Patients in the PIT 1-3 group had a 5-year progression-free survival rate of 47%, compared with only 8% for patients in the PIT 3-4 group (P = .0004). Thus, the City of Hope experience suggests that HDT and analogous HCT can improve long-term disease control in relapsed or refractory PTCL, particularly when applied during first complete or partial remission in patients with favorable prognostic factors.

Table 1. Reduced-Intensity Allogeneic HSCT in Mantle Cell Lymphoma*

Study	N	Median Age, y	Prior ASCT	Preparative Regimen	Event-Free Survival	Overall Survival	Non-Relapse Mortality	Median Follow-Up
CIBMTR 2013 [86]	128	59	33%	Various	25% at 3 years	30% at 3 years	43% at 3 years	43 months
French 2012 [87]	70	54	67%	Flu-based	50% at 2 years	53% at 2 years	32% at 2 years	24 months
BSBMT 2010 [88]	70	48	34%	Flu-based, BEAM	14% at 5 years	37% at 5 years	18% at 1 year	37 months
MDACC 2009 [89]	35	58	17%	FCR (n = 30) or PFA (n = 5)	46% at 6 years	53% at 6 years	9% at 1 year	56 months

*HSCT indicates hematopoietic stem cell transplantation; ASCT, autologous HSCT; CIBMTR, Center for International Blood and Marrow Transplant Research; Flu, fludarabine; BSBMT, British Society for Blood and Marrow Transplantation; BEAM, carmustine, etoposide, cytarabine, melphalan; MDACC, M. D. Anderson Cancer Center; FCR, fludarabine, cyclophosphamide, and rituximab; PFA, cisplatin, fludarabine, and cytarabine.

Table 2. Autologous Hematopoietic Stem Cell Transplantation (HSCT) as Frontline Therapy for Peripheral T-Cell Lymphoma

Trial Group	N	Median Age, y	HSCT Rate, %	Event-Free Survival, %	Overall Survival, %	Non-Relapse Mortality, %	Median Follow-Up
NLG-T-01 2012 [92]	160	55	70	51	51	4	5 years
Korean 2011 [93]	46	47	67	55	57	NR	33 months
German 2008 [94]	83	47	66	36	48	4	33 months
Spanish 2008 [95]	41	47	41	30	39	7	3 years
Italian 2006 [96]	62	43	74	30	34	5	76 months

Chen and colleagues reported similar findings in a retrospective study of 53 patients who received analogous HCT for T-cell lymphomas at Stanford University in Stanford, California [91]. The study population included patients with ALCL (n = 18), PTCL (n = 17), AITL (n = 9), and other NHL subtypes (n = 10). The 5-year rates for progression-free and overall survival were 25% and 48%, respectively. Progression-free survival at 5 years was significantly better for patients who underwent transplantation during first complete or partial remission (51%) compared with second complete or partial remission (12%) or primary refractory disease (0%; $P < .01$). The number of prior regimens also correlated with progression-free survival, with the most favorable outcomes reserved for patients with fewer prior treatments ($P < .01$).

Autologous HTC in Newly Diagnosed PTCL

Another emerging approach designed to improve outcomes in patients with PTCL in first remission is to use transplantation as a form of consolidation therapy. Several prospective clinical trials have examined the use of analogous HCT in the upfront treatment of patients with newly diagnosed PTLC (Table 2). The major limitation of this strategy, however, relates to the low rate of transplantation. Even with strict eligibility criteria for study enrollment, only 41% to 74% of patients are able to undergo autologous HTC.

In 2012, investigators from the Nordic Lymphoma Group reported findings from a prospective phase II study (NLG-T-01) of HDT and analogous HCT in 160 patients with previously untreated systemic PTCL [92]. After excluding patients with ALK-positive ALCL, the study population included patients with PTCL-U (39%), ALK-negative ALCL (19%), AITL (19%), and enteropathy-associated T-cell lymphoma (EATL; 13%). The median age was 57 years (range, 18 to 67 years). Induction therapy consisted of 6 cycles of biweekly CHOEP (or CHOP for patients older than 60 years of age). After induction, 115 patients (70%) achieved a CR or PR and proceeded to consolidation therapy with HDT/analogous HCT.

Results from the NLG-T-01 trial support the use of dose-dense induction followed by HDT/analogous HCT in transplantation eligible patients with previously untreated PTCL. At 5 years, the progression-free survival rate was 44%, and the overall survival rate was 51%. Results were consistent across all histologic subtypes, although there was a nonsignificant trend toward more favorable progression-free survival in patients with ALK-negative ALCL ($P = .26$).

Few studies in PTCL focus on treatment considerations for a single histologic subtype. One notable exception is a study from the Lymphoma Working Party of the European Group for Blood and Marrow Transplantation that examined the use of HDT/analogous HCT in 146 patients with AITL [97]. The key finding from this analysis underscores the importance of transplantation during first CR. Progression-free survival at 48 months was 56% for patients who underwent transplantation during first remission compared with 30% for those with chemotherapy-sensitive disease, and 23% for those with chemotherapy-refractory disease.

Graft-Versus-Lymphoma Effect in PTCL

Limited evidence supports the existence of a graft-versus-lymphoma (GVL) effect following allogeneic HTC in patients with PTCL. One retrospective analysis examined transplantation outcomes in 77 patients with aggressive T-cell lymphomas, including ALCL (n = 27), PTCL-U (n = 27), AITL (n = 11), and other histologic subtypes [98]. Most patients (74%) received myeloablative conditioning prior to transplantation. Donors were HLA-identical and related for 60 patients, HLA-identical and unrelated for 10 patients, and HLA-mismatched unrelated for 7 cases. The 5-year event-free and overall survival rates were 53% and 57%, respectively. A multivariate analysis showed that having an HLA-mismatched donor predicted an increased risk in treatment-related mortality ($P = .04$). The cumulative 5-year risk of treatment-related mortality was 33%.

Given concerns about donor availability for otherwise transplantation eligible patients, there is growing interest in the use of HLA-haploidentical grafts. In 2013, Kanakry and colleges described the feasibility of HLA-haploidentical allografts for patients with PTCL [99]. The retrospective study included 44 patients with PTCL who underwent allogeneic blood or bone marrow transplantation (BMT) with related-donor grafts at Johns Hopkins Hospital in Baltimore, Maryland. RIC was used in 24 patients prior to allogeneic BMT with HLA-haploidentical (n = 18) or HLA-identical (n = 6) grafts. By comparison, 20 patients received myeloablative conditioning followed by BMT with HLA-haploidentical (n = 4) or HLA-identical (n = 16) allografts. Patients in the RIC group were older (median age, 59 years) than those who received myeloablative conditioning (median age, 46 years).

For all patients, the estimated 2-year progression-free survival rate was 40%, and the 2-year overall survival rate was 43%. The 1-year risk of relapse was similar for patients who received myeloablative conditioning followed by HLA-identical allografts (38%) and for patients who received RIC and HLA-haploidentical allografts (34%). The 1-year risk of non-relapse mortality was also comparable across treatment groups, including all recipients of myeloablative conditioning (10%), all recipients of RIC (8%), and the subgroup of RIC patients who received HLA-haploidentical allografts (11%).

Summary

Allogeneic HTC remains the only known cure for MCL, with remissions of 5 years or longer observed in many patients. Evidence to date suggests that intensified induction with rituximab and high-dose cytarabine added to standard induction regimens such as CHOP or hyperCVAD (fractionated cyclophosphamide, vincristine, cytarabine, and dexamethasone) can improve outcomes in

patients with newly diagnosed MCL. Based on current evidence, younger patients with a good performance status should be offered a R-hyper-CVAD- or R-CHOP-like regimen with high-dose cytarabine and then proceed to autologous HTC. Indeed, for patients younger than 65 years of age, regimens containing high-dose cytarabine should be considered the new standard of care for the frontline treatment of MCL.

Although autologous HTC shows minimal benefit for relapsed or refractory MCL, allogeneic HTC can induce durable remissions in patients in relapse following a previous autologous transplantation. For patients with poor prognostic factors, such as a high MIPI score or evidence of Ki67 overexpression, however, even allogeneic HTC provides limited benefits. Novel agents and new therapeutic options are needed to improve outcomes in older patients with MCL and in those with high-risk disease.

In PTCL, autologous HTC is more efficacious when performed in early disease, with the most favorable outcomes observed in patients who undergo autologous HTC during first clinical remission. The use of frontline analogous HCT appears to improve progression-free and overall survival for patients with PTCL, as compared with historical data of CHOP-based chemotherapy alone. Approximately 30% to 50% of patients, however, do not reach transplantation due to progressive disease despite induction therapy.

Myeloablative allogeneic HTC is associated with a high risk of transplantation-related mortality in most hematologic malignancies, and certainly in PTCL. Alternatives to this approach, including the use of reduced-intensity and nonmyeloablative conditioning, appear promising for select patients. Upfront allogeneic HTC may have a role in the treatment of patients with rare high-risk histologies, including hepatosplenic T-cell lymphoma, EATL, and Gamma-delta T-cell lymphoma. Future research is needed to determine whether there is a role for allogeneic HTC as salvage therapy for patients who are beyond complete first or partial remission.

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ASBMT
Blood and Marrow TRANSPLANTATION REVIEWS

ASBMT News

2014 BMT TANDEM MEETINGS: February 26 - March 2

The combined 2014 annual meetings of ASBMT and the Center for International Blood and Marrow Transplant Research (CIBMTR) will be February 26 - March 2 at the Gaylord Texan Convention Center in Grapevine, just north of Dallas, Texas.

Recent advances in the broad field of cellular therapy and blood and marrow transplantation will be addressed in plenary sessions, concurrent sessions, oral abstracts, workshops, poster sessions and symposia.

The scientific program chair for ASBMT is Ginna G. Laport, MD, of the Stanford Hospital and Clinics, Stanford, California and the scientific chair for CIBMTR is Paul J. Martin, MD, of the Fred Hutchinson Cancer Research Center, Seattle, Washington.

In addition to the five days of scientific sessions for BMT clinicians and investigators (February 26 - March 2), there will be other related conferences and sessions (tentative schedule is as follows):

State of the Science Symposium
February 24-25
FACT Workshops for Applicant Preparation and Inspector Training
February 25
Clinical Research Professionals / Data Manager
February 25-26
BMT CTN Coordinators/Investigators
February 25-26
Fundamentals of HCT Training Course/ Pharmacy Boot Camp
February 26-27
Pediatric BMT
February 27
BMT Center Administrators
February 27-28
BMT Pharmacists
February 28-Mar. 1
Transplant Nursing
February 28-Mar. 2
Medical Directors
March 1
BMT Clinical Education Conference (NPs, PAs, Fellows and Junior Faculty)
March 1-2

The deadline for early conference registration and abstract submission is Oct. 10. Online conference registration, abstract submission and housing reservations is now open and can be accessed at both the ASBMT Web site, ***www.asbmt.org***, and the CIBMTR Web site, ***www.cibmtr.org***. Information is updated continuously.

CME Assessment Test

Part I: Multiple Myeloma Treatments for the Transplant-Eligible and Non–Transplant-Eligible Patient

1. **In an analysis of 3 multicenter phase III trials in older patients with multiple myeloma, which depth of response to first-line therapy significantly predicted improved progression-free and overall survival?**
   A. Minimal residual disease by flow cytometry
   B. Complete response
   C. Partial response or better
   D. Stable disease

2. **In a phase III trial of continuous lenalidomide (MPR-R) compared with MPR or MP in patients with newly diagnosed multiple myeloma, lenalidomide maintenance therapy was associated with:**
   A. Prolonged progression-free survival
   B. Improved overall survival
   C. Reduced risk of second primary cancer
   D. Increased risk of treatment-related mortality

3. **In the CALGB 100104 study of lenalidomide maintenance versus placebo following HDT-ASCT in patients with multiple myeloma, lenalidomide maintenance prolonged the time to progression in:**
   A. Patients with prior lenalidomide exposure only
   B. Patients with no prior lenalidomide exposure only
   C. All patients on lenalidomide maintenance, regardless of prior treatment
   D. No patients on lenalidomide maintenance

4. **In the phase III HOVON-65 trial, patients achieved superior progression-free survival with:**
   A. VAD induction, HDT-ASCT, and thalidomide maintenance
   B. PAD induction, HDT-ASCT, and bortezomib maintenance
   C. Neither A nor B; progression-free survival was comparable in both treatment groups

Part II: Transplant and Non-Transplant Therapies for Mantle Cell Lymphoma and Peripheral T-Cell Lymphoma

1. **Most subtypes of PTCL are associated with a poor prognosis, except:**
   A. ALK-positive ALCL
   B. ALK-negative ALCL
   C. PTCL-unspecified
   D. Angioimmunoblastic T-cell lymphoma

2. **In the StiL trial of bendamustine-rituximab (B-R) versus R-CHOP in patients with previously untreated indolent NHL and MCL, treatment with B-R was associated with:**
   6. A. Prolonged overall survival in non-MCL cancers only
   B. Prolonged overall survival in all patient subgroups
   C. Improved progression-free survival in non-MCL cancers only
   D. Improved progression-free survival in all patient subgroups

3. **Ibrutinib is associated with high response rates in the following patients with relapsed/refractory MCL:**
   A. Bortezomib-naïve patients
   B. Bortezomib-exposed patients
   C. All patients, regardless of bortezomib exposure
   D. No patients, regardless of bortezomib exposure

4. **In the MCL Network Trial of patients younger than aged 65 years with previously untreated MCL, which regimen significantly improved response duration**
   A. CHOP x 6 and ASCT
   B. R-CHOP x 6 and ASCT
   C. R-CHOP x 3 → R-DHAP x 3 and ASCT
   D. None of the above

5. **According to data from the CIBMTR registry, overall survival is highest in patients with MCL following:**
   A. Autologous HSCT
   B. HLA-identical sibling donor allogeneic HSCT
   C. HLA-identical unrelated donor allogeneic HSCT
   D. HLA-mismatched unrelated donor allogenic HSCT

6. **Which of the following is associated with improved event-free and overall survival outcomes following allogeneic HSCT in patients with MCL?**
   A. Myeloablative conditioning regimen
   B. Reduced-intensity conditioning regimen
   C. Transplant during first complete remission
   D. Exposure to ≥ 2 prior chemotherapy regimens

CME Evaluation Form

Please evaluate the effectiveness of this CME activity on a scale of 1 to 5, with 5 being the highest, by circling your choice. Fax *with the Answer Sheet* to the Office of Continuing and Professional Education, 414-456-6623, or mail to the Office of Continuing Medical Education, Medical College of Wisconsin, 10000 Innovation Drive, Milwaukee, WI 53226.

Overall Quality of the CME Activity	1	2	3	4	5
Articles in the publication were presented in a clear and effective manner.	1	2	3	4	5
The material presented was current and clinically relevant.	1	2	3	4	5
Educational objectives were achieved.	1	2	3	4	5
The CME activity provided a balanced, scientifically rigorous presentation of therapeutic options related to the topic, without commercial bias.	1	2	3	4	5

How will you change your treatment based on this CME activity?

Would you benefit from additional CME programs on this topic? Yes No

I have read these articles on The Impact of Reduced-Intensity Conditioning Regimens in Transplant Outcomes, published in *Blood and Marrow Transplantation Reviews*, and have answered the CME test questions and completed the Evaluation Form for this activity.

Signature Date

Last Name	First Name	MI	Degree
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CME Assessment Test Answer Sheet – Program ID #13203

Release Date: July 12, 2013
Last Review Date: July 12, 2013
Expiration Date: July 12, 2014

Instructions

(1) Read the articles in the publication carefully. (2) Circle the correct response to each question on the Answer Sheet. (3) Complete the Evaluation Form. (4) To receive CME credit, fax the completed Answer Sheet and Evaluation Form to the Office of Continuing and Professional Education (414-456-6623) or mail to the Office of Continuing Medical Education, Medical College of Wisconsin, 10000 Innovation Drive, Milwaukee, WI 53226. No processing fee is required.

Part I

1.	A	B	C	D
2.	A	B	C	D
3.	A	B	C	D
4.	A	B	C	

Part II

1.	A	B	C	D
2.	A	B	C	D
3.	A	B	C	D
4.	A	B	C	D
5.	A	B	C	D
6.	A	B	C	D

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