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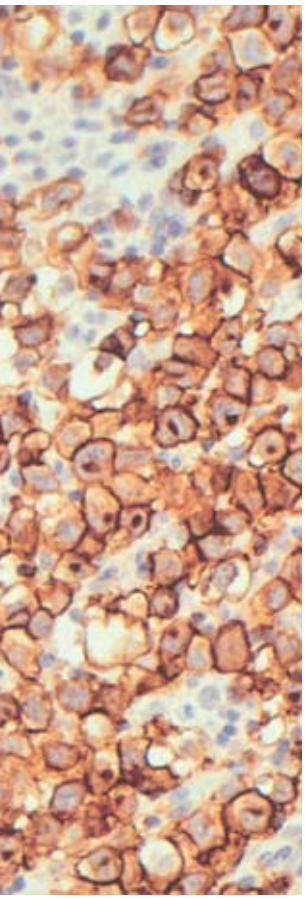

How The Experts Treat Hematologic Malignancies: A Roadmap to Treatment

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OVERVIEW

By the end of 2009, it was estimated that 65,000 people were living with multiple myeloma, 675,670 with lymphoma, and 290,015 with or in remission from some form of leukemia. Given the frequency of the occurrence of these diseases and the complexities of their individual clinical presentations and courses, there is a need for primary care and specialty physicians to engage in an in-depth examination and discussion of the emerging data that underlie optimal management of these patient populations. Comprehensive Cancer Centers remain at the forefront in their generation and application of these emerging data to improve patient outcomes.

TARGET AUDIENCE

This activity is intended for hematologists, medical oncologists, radiation oncologists, hematology/oncology fellows, oncology nurses, and other allied health care professionals who will benefit from a review and update on the latest advances in the diagnosis and treatment of lymphoma, leukemia, and multiple myeloma.

LEARNING OBJECTIVES

At the conclusion of this educational activity, participants should be able to:

- Evaluate the new molecular and immunologic treatment being developed for hematologic malignancies
- Demonstrate the rationale for new targeted diagnostic and evolving therapeutic strategies used in the care of patients with lymphoma, myeloma, acute and chronic leukemia, and myelodysplasia
- Interpret the role and timing of hematopoietic cell transplantation in the management of younger and older patients' hematologic malignancies
- Summarize the evolving therapeutic strategies in the treatment of hematologic malignancies

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CONTENTS

How I Treat Follicular Lymphoma

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INTRODUCTION

The question of what is the best approach to the treatment of patients with follicular lymphoma (FL) has been controversial in the past, and in some ways this situation has not changed for patients with this disease today. FL is relatively easy to diagnose and often has an indolent disease course. In some cases it is uncertain whether patients actually benefit from treatment or may be better served by a watch-and-wait approach. Disease progression remains a risk, however, and strategies used to address this threat are varied. Decisions regarding the management of FL have taken on a new perspective with the advent of treatments that offer the hope of prolonged survival and even a cure.

Diagnosis and follicular lymphoma

FL is the most reproducibly diagnosable lymphoma. Expert pathologists who diagnosed a variety of lymphomas had the highest percentage of agreement on the diagnosis of FL. A reliable diagnosis was made solely on the basis of histological analysis of slides of stained tissue samples, one of the few instances in lymphoma pathology in which secondary diagnostic procedures were not required. FL varies in presentations and processes, however, and determining the best treatment continues to be challenging for physicians and their patients.

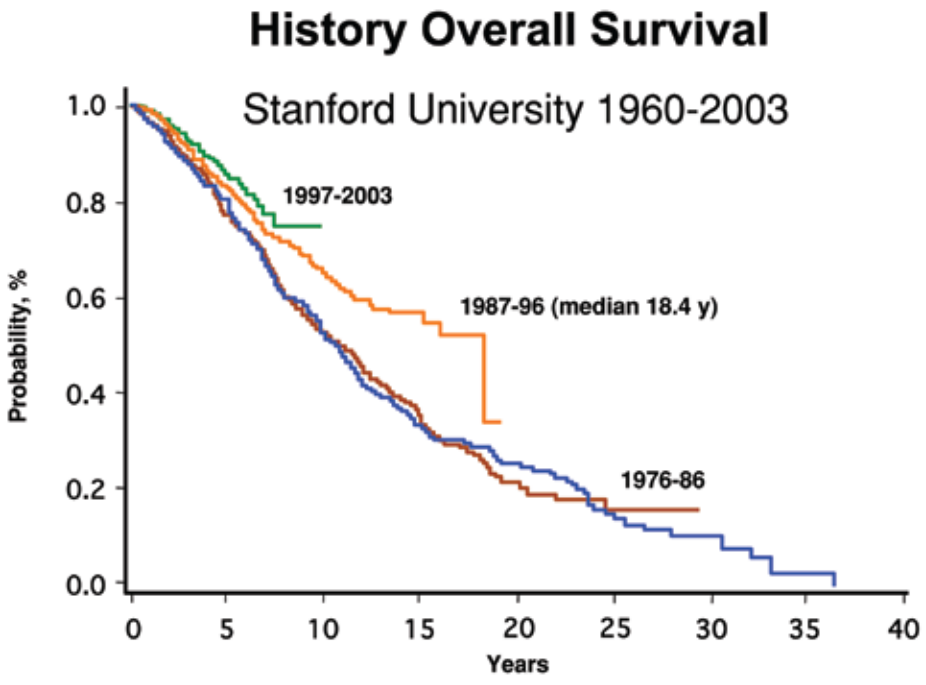
TYPES OF FOLLICULAR LYMPHOMA

Cutaneous, duodenal, and pediatric FL are all characterized by slow progression. In many cases, local treatment is successful, or treatment may not be required. Unlike nodal FLs, cutaneous FLs can often be successfully treated simply by excision. FLs of the duodenum, which seem to differ from FL found at other visceral extranodal sites, are unusually indolent diseases and often can be followed without therapy. Pediatric FL is a rare disease that has an extremely indolent process and can often be treated locally with no other therapy.

Despite their high level of agreement in identifying FL, pathologists asked to subdivide various types by using the most objective system, the Bérard system, could reproducibly assign grade 1, grade 2, and grade 3 only about two-thirds of the time. FL grade 3 can be further differentiated as either type 3A, a more indolent form, or 3B, considered by some to be the same as diffuse large B-cell lymphoma. In general, however, FL grade 3 is a disease that is quite different from grades 1 and 2, with more highly proliferative tumors that warrant more aggressive treatment. In patients with FL grade 3, cyclophosphamide, adriamycin, vincristine, and prednisone (CHOP)-like chemotherapy regimens used for diffuse large B-cell lymphoma may be effective [1,2].

DISEASE STAGING AND TREATMENT

From a practical point of view, 2 stages for FL are localized disease, which can be treated with radiation, and disseminated disease. According to the Follicular Lymphoma International Prognostic Index (FLIPI), more advanced-stage disease is indicated by the presence of ≥5 nodal sites, elevated lactate dehydrogenase, age ≥60 years, Ann Arbor Stage III or IV tumor, and hemoglobin <12 mg/dL [3].



Improved survival in patients with follicular lymphoma (FL) treated with rituximab. Image courtesy of Dr. Sandra Horning.

An issue that has been a point of debate for quite a long time is whether therapy affects overall survival in patients with grades 1 and 2 FL, particularly patients who are asymptomatic. Data from the 1960s to the mid-1990s indicated that treatment did not make any impact on the ultimate survival of patients with FL [4]. Recently, however, survival rates for FL have been improving (Figure). Data from SEER (US National Cancer Institute's Surveillance, Epidemiology, and End Results Program) [5] demonstrated a significant improvement in the median survival of patients with FL in the United States.

RITUXIMAB TREATMENT FOR FOLLICULAR LYMPHOMA

The overwhelming evidence supports the idea that the addition of the immunotherapeutic drug rituximab to our treatment of FL patients is the most important factor associated with the apparent improvement in survival (Figure) [6]. The effectiveness of rituximab seems to involve several mechanisms. There is no question that it can directly kill tumor cells, but it might alter the tumor microenvironment as well.

TREATMENT REGIMENS

Patients who require treatment most commonly receive rituximab in combination with chemotherapy. The most effective chemotherapy regimens are rituximab in combination with cyclophosphamide, vincristine, and prednisone with rituximab (CVP-R); CHOP with rituximab (CHOP-R); and combinations that include fludarabine or bendamustine. Recent data, however, have shown that patients treated with CHOP-R had 10% improved progression-free survival compared with patients treated with CVP-R [7]. After these treatments, maintenance therapy with rituximab has been show to increase remission time and should become standard therapy.

Is there still a place for "watch and wait?" Randomized trials have never shown a disadvantage to initial observation in asymptomatic patients, but trials have not been done with rituximab in the treatment arm. In practice in the United States, single-agent rituximab is replacing watch and wait.

CONCLUSIONS

Our treatments for FL are getting better, and there are patients who survive for a very long time free of the disease. Some patients with FL probably can be cured.

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How I Treat Diffuse Large B-Cell Lymphoma

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INTRODUCTION

The development of curative combination chemotherapy for patients with advanced stages of aggressive non-Hodgkin's lymphomas such as diffuse large B-cell lymphoma (DLBCL) is one of the major successes of cancer therapy. First-generation regimens, which generally include 4 chemotherapeutic agents, produce complete remission in 45% to 55% of patients and cure in approximately 30% to 35%. Among these first-generation regimens, cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) was studied extensively in national cooperative-group trials and has long been considered the standard therapy. In a study published in 1993 in which we compared CHOP with third-generation regimens, we confirmed that CHOP was the best available treatment [1]. On the basis of these results, it seemed unlikely that the use of different combinations of existing drugs would significantly improve the results of therapy. We concluded that innovative approaches were needed and that the efficacy of any promising new treatment program would have to be assessed by comparing it with CHOP in randomized clinical trials.

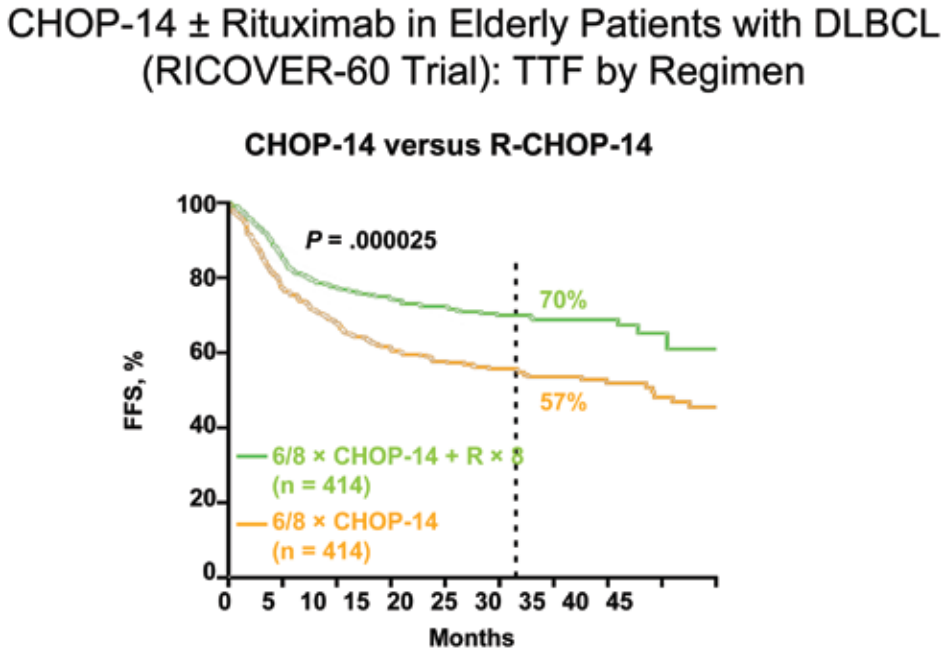
RITUXIMAB IN THE TREATMENT OF DIFFUSE LARGE B-CELL LYMPHOMA

Rituximab has changed the prognosis and treatment paradigm for all patients with DLBCL [2]. Rituximab is a chimeric monoclonal antibody that binds specifically to the CD20 antigen. Because most B-cell lymphomas express the CD20 antigen, the use of rituximab was investigated in the treatment of patients with DLCL in the first study to evaluate the efficacy and the safety of an anti-CD20 monoclonal antibody therapy in patients with aggressive lymphoma [3]. Diffuse large cell lymphoma (DLCL) patients experienced significant clinical activity, with response rates to rituximab of 37% and low toxicity. The authors concluded that rituximab had significant activity in DLCL and should be tested in combination with chemotherapy in such patients. Surprisingly, when rituximab is combined with CHOP, for reasons that are still unclear, there is a synergistic benefit, ie, more than the additive effect of the rituximab alone. Rituximab is relatively ineffective as a single agent in DLCL.

Age >60 years is a risk factor for inferior outcome in DLBCL, but in previously untreated DLBCL patients 60 to 80 years old, the addition of rituximab to standard CHOP chemotherapy (R-CHOP) significantly reduced the risk of treatment failure and death, without clinically significant greater toxicity (Figure) [4]. At this time, however, data do not support the use of dose-escalated CHOP in older patients.

RADIATION TREATMENT IN DIFFUSE LARGE CELL LYMPHOMA

During the past decade, combined treatment with brief-duration chemotherapy with subsequent involved field radiation has evolved to become the reasonable standard of care for most patients with early stage DLBCL [5]. For most patients, outstanding results have been reported using this approach. However, outcome data in the rituximab era are raising questions regarding the optimal induction chemotherapy regimen and the role of involved field radiation for most patients.



Study protocol for a clinical trial that demonstrated the effectiveness of rituximab added to treatment of diffuse large B-cell lymphoma (DLBCL) patients 60 to 80 years old. CHOP indicates cyclophosphamide, doxorubicin, vincristine, and prednisone; R-CHOP, rituximab CHOP.

The MInT (MabThera International Trial) trial [6] enrolled young DLBCL patients with favorable risk factors. In early follow-up in the 75% of patients with early stage disease, outstanding results were observed with 6 cycles of CHOP-like chemotherapy and rituximab without radiation (except to bulk disease). These and other data suggest that the benefit of rituximab in early stage DLBCL may have a similar magnitude to the benefit of radiation. Given both short- and long-term toxicities of radiation, efforts are therefore underway to define a group of patients who do not require radiation therapy.

On the basis of available data, we currently recommend 3 cycles of CHOP and rituximab with involved-field radiation for most patients with stage I and nonbulky stage II disease. Six cycles of R-CHOP chemotherapy without radiation appears to be another effective option in patients without bulky disease. Patients with bulky disease clearly require more chemotherapy, and may benefit from intensified regimens.

Advanced-stage DLBCL is a curable disease when treated with systemic chemotherapy. Rituximab has dramatically improved the outcome of advanced-stage DLBCL; when combined with CHOP chemotherapy patients in all risk groups have demonstrated benefit overall survival. Long-term follow-up has revealed significantly improved event-free survival, progression-free survival, disease-free survival, and overall survival in patients treated with R-CHOP, making this the standard of care in DLBCL. Currently, however, maintenance rituximab does not have a therapeutic role in DLBCL.

FUTURE TREATMENTS FOR DIFFUSE LARGE B-CELL LYMPHOMA

Despite the success of rituximab, a significant minority of patients with advanced stage disease and clinical risk factors will not be cured with R-CHOP–based therapy. DLBCL is a heterogeneous disease, and increased insight into the molecular heterogeneity of DLBCL is beginning to yield therapies targeted to specific DLBCL subtypes. Unfortunately however, patients with the prognostically unfavorable activated B-cell subtype of DLBCL also have a less favorable response to R-CHOP. Although transplantation may be an option for some patients, at least half of patients may not be eligible for this approach given advanced age or medical comorbidities. Thus, major improvements in the treatment of DLBCL will include the incorporation of novel, rationally targeted agents into the standard treatment paradigm.

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How I Treat Peripheral T-Cell Lymphoma

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INTRODUCTION

Peripheral T-cell lymphoma (PTCL) is not a single disease but a heterogeneous group of aggressive mature T-/natural killer (NK)-cell lymphomas for which diagnosis is difficult and standard therapies are not yet available. T- and NK-cell lymphomas may be characterized as cutaneous, nodal, extranodal, or leukemic disseminated. T-cell lymphomas make up about 8% to 12% of all non-Hodgkin's lymphomas. The "peripheral" in PTCL does not refer to anatomic sites but rather to the involvement of more mature (postthymic) T-cells versus prethymic or immature T-cells.

PTCL DIAGNOSIS

The classification of PTCL, is an evolving field [1], and PTCL has many subtypes (Figure). Diagnosis of PTCL routinely involves immunophenotypic analysis in conjunction with cellular morphology, analysis of lymph node architecture, and molecular genetic assays. PTCL has many characteristics that make diagnosis challenging, and approximately 10% of PTCL cases are incorrectly diagnosed [2]. PTCLs are predominantly extranodal diseases, which makes biopsy difficult, with small samples that may show some necrosis or angioinvasion, resulting in an inconclusive biopsy. There is no consistent psychologic feature that can be used to distinguish a malignant from a benign-looking T-cell. Cytologic features of PTCL are inconsistent and may overlap with those of nonmalignant infiltrates. There are no immunophenotypic markers of clonality, and there is no diagnostic immunophenotype. PTCLs are nonspecific in response to antigen-receptor (T-cell receptor) assays, and monoclonality does not always indicate malignancy. Few typical chromosomal translocations have been identified for PTCL.

Current National Comprehensive Cancer Network (NCCN) guidelines for hematopathological diagnosis of PTCL stipulate that the diagnosis of PTCL should be performed by a hematopathologist who has experience in diagnosing these conditions [3]. For accurate diagnosis it is important to obtain an excisional biopsy specimen with as much tissue as possible. Specimen analysis should include immunophenotyping and flow cytometric analysis of surface markers. The clinical presentation of the patient should also be taken into consideration.

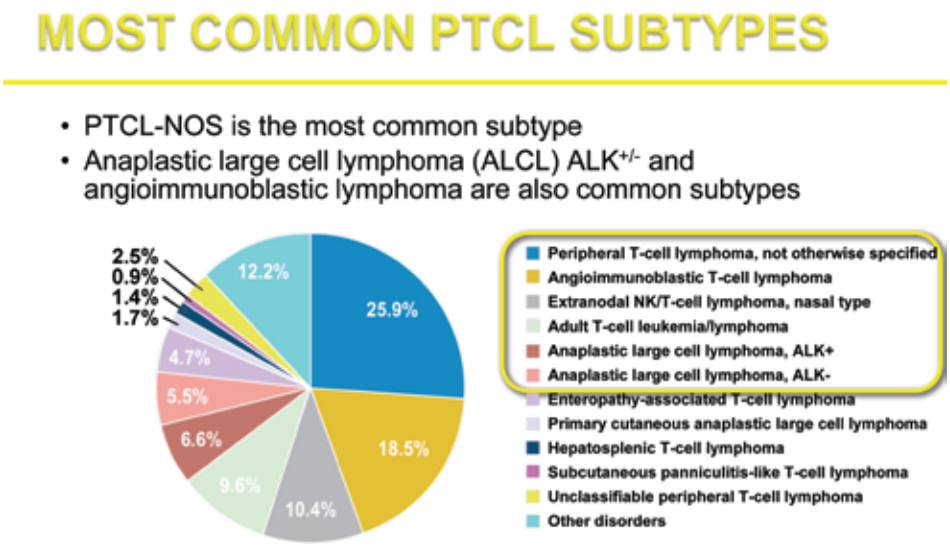
PTCL TYPES AND PROGNOSIS

In general, the presence of a T-cell marker or T-cell lymphoma indicates a poor prognosis. The median overall survival for most subtypes of PTCL is less than 3 years. The worst prognosis is for patients with adult T-cell lymphoma, most of whom die within the first 2 years after diagnosis. Subclassification of PTCL based on the expression of the gene signatures is an important area of investigation. Anaplastic lymphoma kinase (ALK) protein expression can be picked up by immunohistochemical stain and is an important prognostic indicator. Patients with anaplastic large cell lymphoma (ALCL) positive for ALK (ALCL ALK+) have a 5-year survival of 65% to 90%.

The incidence of PTCL shows geographic variation throughout the world. There are parts of far east Asia as well as the Caribbean where there is a higher incidence of virally related lymphomas and some of the NK T-cell lymphomas.

TREATMENT OF PTCL

Treatment of patients with nodal T-cell lymphoma is very challenging. Compared to patients with B-cell non-Hodgkin's lymphoma, patients with PTCL are more likely to present with disseminated disease, B symptoms, bone marrow–positive disease,



Peripheral T-cell lymphoma (PTCL) is a heterogeneous disease with many subtypes. NK indicates natural killer; ALK, anaplastic lymphoma kinase [1]. Reprinted with permission. © 2008 American Society of Clinical Oncology. All rights reserved.

and skin lesions, and treatment paradigms derived from B-cell lymphomas are inadequate. So whenever possible, patients should be enrolled in clinical trials.

According to 2010 NCCN guidelines [3], optimal first-line therapy for NK/T-cell lyphoma with localized presentation is controversial. The options are a short course of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP)/CHOP-like therapy followed by involved-region radiation therapy (IRT); steroids, methotrexate, ifosphamide, L-asparaginase, and etoposide (SMILE) followed by IRT; and dose-adjusted etoposide, vincristine, doxorubicin, cyclophosphamide, and prednisone (EPOCH) for up to 3 cycles followed by IRT. For advanced disease the optimal treatment is not established, and CHOP-based regimens are associated with poor outcomes. Recommended options are aggressive regimens containing L-asparginase, such as SMILE. All patients who achieve complete remission, except those with International Prognostic Index low-risk disease and those with ALK+ ALCL, should be considered for high-dose therapy and autologous stem cell transplantation, which have produced long-term overall and disease-free survival. Unfortunately, however, only 45% to 70% of patients will actually achieve complete remission. Currently, there is no established role for maintenance therapy in PTCL. Treatment agents under investigation include lenalidomide, pralatrexate (10-propargyl-10-deazaaminopterin), and monoclonal antibody.

Allogeneic stem cell transplantation using reduced-intensity conditioning can provide a graft-versus-lymphoma effect and result in long-term remission in eligible patients, even those with relapsed/refractory disease [4]. The antifolate pralatrexate is the only agent that is currently FDA approved for the treatment of relapsed PTCL. This drug is retained within the cell at a higher rate and has higher cytotoxic activity than methotrexate. Its effectiveness in T-cell lymphomas was demonstrated in the large, multicenter, single-arm Pralatrexate in Patients with Relapsed or Refractory Peripheral T-Cell Lymphoma (PROPEL) trial [5].

CONCLUSIONS

Well-designed prospective studies are needed to determine the optimal therapy for PTCL. Because of the rarity of these diseases, effective studies require multicenter collaboration to ensure adequate patient numbers. The unique clinicopathologic features of different subtypes may require different therpeutic approaches for PTCL; one model does not fit all. In the future, combination therapies using novel targeted agents will provide the backbone for upfront therapies, treatment of relapsed disease, transplantation regimens, and maintenance therapies.

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How I Treat Cutaneous T-Cell Lymphoma

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INTRODUCTION

Cutaneous T-cell lymphoma (CTCL) has cosmetic consequences and comfort issues as well as being life threatening. The treatment of CTCLs is very challenging because there are so many treatment options. The best interests of the individual patients and what is realistic for them must be considered, with the recognition that every available treatment will probably be used at a certain juncture.

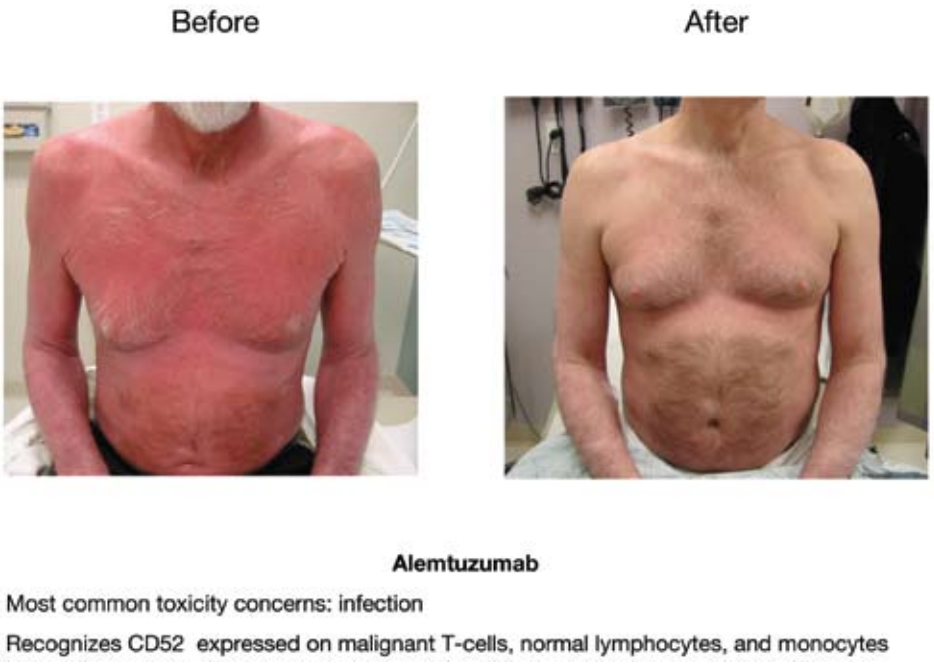
TYPES OF CUTANEOUS T-CELL LYMPHOMA

Of the indolent CTCL variants, the most common is mycosis fungoides, a low-grade lymphoma with postthymic T-cells that express CD4. This disease has a relatively good 5-year survival. Patients present with patch, plaque, or tumor lesions. Some patients present with a de novo tumor, which indicates more aggressive disease. Sézary syndrome is the systemic and aggressive variant of mycosis fungoides. Patients have exfoliative erythroderma; ectropion, often with constant tearing; alopecia; and palmoplantar keratoderma, which can be incapacitating. Patients suffer severe pruritus that is relieved only by disease treatment, not by standard antiitching drugs. This disease is characterized by a circulating atypical malignant lymphocyte with a characteristic phenotype, a postthymic T-cell that is CD3 and CD4 positive, and a number of these markers are targets for therapy, such as CD4 and CD25. In 2005, the abbreviated 5-year survival in patients with this disease was 24%; since then, survival data suggest improvement in the 5-year overall survival. Chromosome aberrations are universal in CTCL, but there is no signature chromosome abnormality.

TREATMENT OF CUTANEOUS T-CELL LYMPHOMA

Quality of life is the key issue in treating CTCL. The risk-benefit ratios must be considered with every treatment decision. Cost can be a major concern in a disease with which the patient may live several decades but must be on constant therapy of some sort. Treatment availability is another concern. Patient evaluation includes physical exam, evaluation of a skin biopsy specimen, immunohistochemical analysis, a blood count and complete chemistry panel, and lactate dehydrogenase, which in the majority of these patients is normal at presentation. Some cases may require flow cytometry and molecular testing for T-cell–receptor gene rearrangements that may be supportive of the diagnosis.

Currently, cure is possible only in patients who present with stage 1A disease, with limited patch disease on <10% of the body surface [1]. In these patients survival is not very different from that of an actuarial healthy match control population. Some patients may be cured by allogeneic transplantation. Only a minority of patients get a durable complete remission. Partial remission is frequently obtained, and ideally the individual has a reasonable quality of life. In one of the few randomized trials performed in this disease, patients were randomized to sequential topical therapy or to a very aggressive program with 8 different chemotherapy drugs and total body skin electron beam radiation. The study showed no apparent advantage to this very aggressive approach. In fact, in patients with the most advanced disease, the more aggressive approach had a worse prognosis. As a result, most of us in the field started to do sequential palliative treatment [2].



Patient response to alemtuzumab treatment.

Topical treatments are the first choice for limited-stage disease. These include topical corticosteroids, which have a high response rate and are convenient and inexpensive, and topical chemotherapy, such as nitrogen mustard, which has been around for several decades, and carmustine, which is equally effective in treating the disease, but can cause telangiectasia, which may be a worse cosmetic problem than the original disease. Topical retinoids, in particular bexarotene, can be used only on isolated patches, not the total body, because of irritation and also high cost.

Phototherapy has a high response rate, with a partial or a complete response in 79% to 90% of patients. Many of these are long-term responses. Phototherapy may involve either narrow-band UVB light, or PUVA therapy, in which the patients ingest a furocoumarin molecule called psoralen approximately 1.5 hours before exposure to UVA light. The psoralen compound can cause nausea, so patients take it with food and sometimes with an antiemetic. Phototherapy patients must be screened regularly for secondary skin cancers.

Total body electron beam radiation therapy is used because electrons have limited depth of penetration, so you can treat the skin with minimal internal radiation. This method is effective but technically very challenging. Most patients ultimately relapse, and then it becomes very difficult to treat them. Site-directed radiation is frequently used for isolated recalcitrant lesions.

Off-label therapies used topically include the interferon-inducer imiquimod and the antiinflammatories pimecrolimus and tacrolimus, in particular for lesions are on the face.

Systemic therapies include steroids, which are very effective in inducing remission, but remissions are variable and steroid toxicity is a problem. System steroids are useful mainly for brief periods in select instances in which pruritus may be disabling or in a patient with progression to buy some time before the next therapy.

NEW TREATMENTS FOR CUTANEOUS T-CELL LYMPHOMA

A number of agents have been approved over the last decade for the treatment of mycosis fungoides and Sézary's syndrome, including interferon, which we feel is the most active drug in the disease. The topical form and oral forms of the proteasome inhibitor bexarotene also have activity in CTCL. Denileukin diftitox is a new targeted therapy. Aletuzumab has been a wonderful addition to the armamentarium, and the humanized anti-CD4 also has activity.

Chemotherapy drugs used for any non-Hodgkin's lymphoma tend to work, such as alkylating agents. Methotrexate is oral, well tolerated, and has a high response rate. There is some suggestion that pralatrexate will work in methotrexate-resistant patients. The nucleoside analogs all have some activity, particularly gemcitabine, and now there is work with forodesine, a promising phosphorylase inhibitor. Doxorubicin is very effective because of its skin-homing activity.

Extracorporeal photochemotherapy (ECP), or photopheresis, involves removal of approximately a pint of the patient's blood, from which the white cells are isolated and exposed to a psoralen-like compound bath, treated with ultraviolet light, and then infused back into the patient along with the normal red blood cells. Two sessions in a row are done every 2 weeks until remission is seen, and then once a month. Patients with low levels of circulating cells who have erythroderma have the highest response rates, and some patients with patch disease who have circulating cells seem to benefit. A number of investigators are combining other biologics with the photopheresis. Alemtuzumab, which has shown high response rates in erythrodermic patients, can be administered subcutaneously, is very effective and along with photophoresis is one of the selective approaches for Sezary Syndrome patients.

TREATMENT SEQUENCES IN CUTANEOUS T-CELL LYMPHOMA

At our center, results have supported consideration of aletuzumab for use as initial therapy, which sometimes has dramatic results (Figure). Then, as the disease progresses, or if it presents in a more aggressive form, we use psoralen plus ultraviolet light of A wave length (PUVA) with or without interferon, or low-dose retinoids. In some instances, we us retinoids alone or the histone deacetylase inhibitors vorinostat and romidepsin. If the disease continues to progress, we often proceed to allotransplantation. Combination chemotherapy can be used in preparation for transplantation. We have rarely done autologous transplantation. Most transplantations we perform are allogeneic, and a number of these patients have done well for more than a decade. Most recently we have been doing a lot of nonmyeloablative transplantation. In patients who present with erythroderma, we do photopheresis, plus or minus interferon, or bexarotene.

Interferon treatment has a slow response, with typical side effects of malaise, fatigue, nausea, and skin toxicity. Another adverse effect to ask male patients about is erectile dysfunction. General skin care is important and includes monitoring for *Staphylococcus aureus* colonization. Patients should use unscented soaps and antiseptic skin cleansers, skin moisturizers that preserve the skin barrier, and supportive antipruritic medications, which may give some relief. Bleach baths are another option. In general, while managing CTCL with the variety of available agents, the focus must be on the whole patient in this disease in particular because of the issues related to comfort, body image, and intimacy.

CONCLUSIONS

Patients with CTCLs suffer physical discomfort as well as cosmetic concerns. Effective palliative treatments are available, but cure is rare and the cost of ongoing treatment is a concern during a long disease course. Recent promising results in clinical trials of new treatment agents such as anti-CD30 monoclonal antibodies offer hope for a better future.

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How I Treat Hodgkin's Disease

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INTRODUCTION

Hodgkin lymphoma (HL) can now be cured in the majority of patients, 90% to 95% of patients with early stage HL with favorable prognostic indicators and 70% to 85% of patients with advanced HL. A powerful tool in the management of HL treatment is positron-emission tomography (PET) scanning, which can be used to predict how the disease will behave in individual patients, but studies must be conducted to deter-mine how that information should be used and develop protocols adapted to PET-driven response data.

HODGKIN'S LYMPHOMA DIAGNOSIS

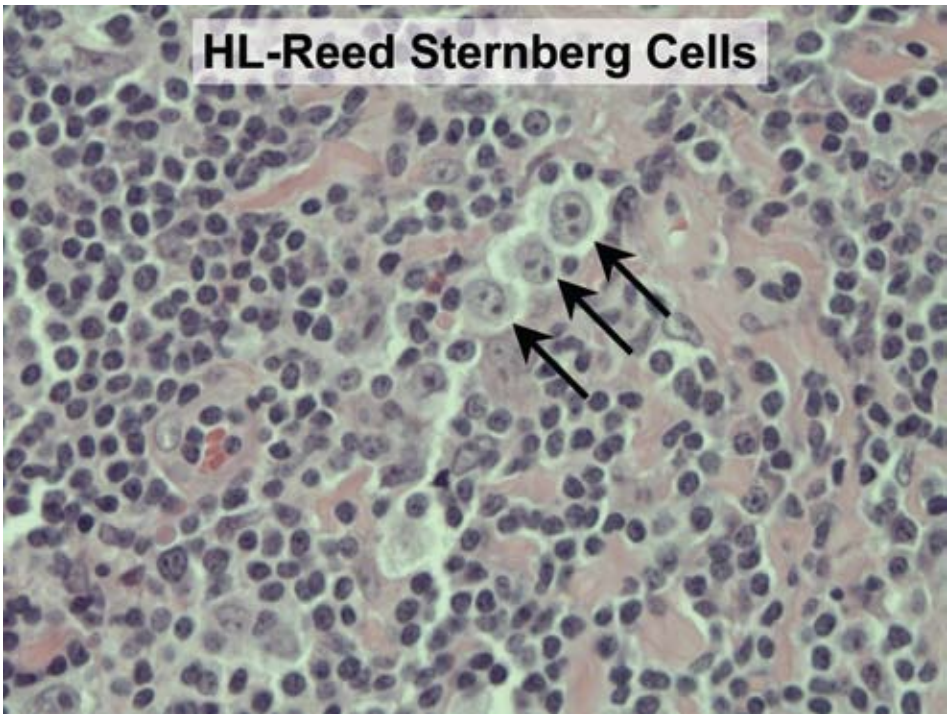
The diagnostic workup for HL is based on an excisional or large-core biopsy specimen, which will reveal typical Reed Sternberg cells (Figure). In most cases, Reed Sternberg cells from classical HL express CD15 and CD30 but not CD20, whereas the malignant cells in nodular lymphocyte-predominant HL express CD20 and other mature B-cell markers but usually not CD15 or CD30.

Routine laboratory tests are helpful, particularly hemoglobin, albumin, and sedimentation rate, as well as HIV testing, since HL is one of the lymphomas that is increased in HIV-positive patients. Contrast-enhanced computed tomographic (CT) scans are still the standard approach for measuring diseases response; however, the routine use of PET at diagnosis and at the end of therapy is now also standard. Data suggest that interim PET scanning has prognostic value and that patients who are PET-negative after 2 cycles of chemotherapy will do well regardless of their International Prognostic Score. In the HL patient population, which is typically young, it is very important to emphasize counseling regarding fertility, including options for sperm, ova, or embryo cryopreservation. Because of the increased risk of cardiovascular disease, patients should be advised to diminish other risk factors, particularly smoking.

There are several subtypes of classic HL, but because the treatment is fairly similar for all of these subtypes, specific categorization is less important now than it was in an earlier era. However, it is still important to differentiate nodular-lymphocyte predominant HL, which has different management considerations, excellent overall survival (90% to 95% at 20 years), and responds to new agents such as rituximab, which are generally not effective in classical HL.

TREATMENT OF EARLY STAGE FAVORABLE AND UNFAVORABLE HODGKIN LYMPHOMA

On the basis of findings of the German Hodgkin Lymphoma Study Group (GHSG), early stage HL can be divided into favorable and unfavor-able HL categories. Favorable disease is characterized by 1 or 2 sites of involvement without a large mediastinal mass and no bulk greater than 10 cm, with a normal sedimentation rate and no extranodal sites. Patients with stage I-II "favorable" HL can be treated with less intensive and less toxic therapy consisting of a short course of adriamycin (doxorubicin), bleomycin, vinblastine, dacarbazine (ABVD) and involved-field radio-therapy (IFRT). The number of cycles of ABVD that should be administered has been debated, with the GHSG reporting that as few as 2 cycles of ABVD and as low as 20 Gy of IFRT are adequate for early stage favorable HL [1]. There are concerns even for 20 Gy radiotherapy, however, particularly in young women, who have a significant risk of later development



Reed Sternberg cells are a biopsy finding that is diagnostic for Hodgkin's lymphoma (HL).

of breast cancer. Therefore, some oncologists prefer to omit radiotherapy altogether, and administer more cycles of ABVD. This approach is still controversial and is being investigated in trials using PET to assess the effectiveness of treatment.

More therapy is required in patients with early stage "unfavorable" HL, characterized by stage I and II disease with adverse features such as 3 or more sites of disease, bulky disease, a high sedimentation rate, or extranodal sites. Generally these patients should be treated with 4 to 6 cycles of ABVD and then IFRT at a dose of 30 Gy.

ADVANCED HODGKIN LYMPHOMA

Advanced HL includes stages III and IV, bulky stage II, and IIB with poor response. Clinical trial participation is recommended in this group of patients, otherwise treatment with ABVD for 6 to 8 cycles is recommended. The question of whether to give consolidative radiation to areas of prior bulk in advanced HL is controversial, but current randomized trial data indicate that it is probably not necessary. The basis for the standard ABVD regimen used in the United States and most other countries is the study by Canellos et al reported in 1992 [2], with a recently pubished 20-year update [3] showing that the results still pertain for event-free survival with very long follow-up. Regimens more intense than ABVD are available, with the most promising regimen being bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone (BEACOPP-escalated). This very intense regimen doubles the etoposide dose and increases the doxorubicin and cyclophosphamide doses compared to the original BEACOPP-standard regimen. BEACOPP-escalated has shown superiority in terms of freedom from treatment failure and overall survival compared to ABVD and BEACOPP-standard, however, concerns about the toxicity of the regimen, in particular hematologic toxicity, gonadal toxicity, and the induction of secondary malignancies have hampered its widespread adoption outside Germany. With ABVD, virtually all patients remain fertile or regain fertility; however, with more intense regimens such as BEACOPP-escalated, the majority of patients become infertile. ABVD-based regimens also have a decreased risk of acute myelogenous leukemia, myelodysplasia, and hematologic and nonhematologic toxicity and cure 70% of patients. An ongoing trial that is still accruing patients with advanced stage HL seeks to use PET scans to identify the 30% of patients who will not do well with ABVD alone, and then make an early switch after 2 cycles to BEACOPP-escalated.

Although the Stanford V regimen (bleomycin, doxorubicin, etoposide, mechlorethamine, prednisone, vinblastine, and vincristine) was previously touted as an advance compared to ABVD, recent randomized trials show that ABVD is as effective and less toxic than Stanford V.

LONG-TERM FOLLOW-UP AND RELAPSE AFTER HL TREATMENT

Patients who have been treated for HL are at risk for the development of late adverse effects including second malignancies resulting from chemotherapy and radiation, cardiac disease, endocrine dysfunction, infertility, hypothyroidism, psychological trauma, lung damage (usually subclinical), hyposplenism, and dental caries. Recommended follow-up includes physical examination, laboratory tests, chest x-ray or chest CT, abdominal and pelvic CT, and psychological counseling. Surveillance PET scans are not recommended because of the high incidence of false-positive results in patients who are in complete remission following therapy.

Treatment of relapsed HL includes chemotherapy for 3 or 4 cycles with a regimen such as ICE (Ifosfamide, carboplatinum, and etoposide) with collection of peripheral blood stem cells after the second cycle, and then high dose chemoradiotherapy with autologous stem cell transplan-tation. Options are limited for recurrence after autotransplantation, so clinical trial enrollment is recommended. New salvage treatments include the antibody drug conjugate SGN-35 and the GVD regimen (gemcitabine, vinorelbine, and doxorubicin). Nonmyeloablative allogeneic transplantation has also demonstrated considerable promise in patients who have recurred after an autologous transplant.

CONCLUSIONS

It is important to emphasize that all of the improvements in the treatment of HL and most other lymphomas have occurred because of clinical trials, and clinicians are strongly encouraged to enroll as many patients as possible in ongoing trials so that treatment will continue to improve.

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How I Treat Multiple Myeloma

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INTRODUCTION

In the past, treatment of multiple myeloma (MM) did not involve risk stratification, and effective drugs were limited. With the availability of improved treatments, choices have become more complicated. For aggressive disease the first choice is a regimen that has a rapid and deep response, and all of the new, novel agents can give high response rates. Questions that remain to be answered include whether to use therapeutic rationing by giving drugs in sequence or to combine the most effective drugs up front followed by transplantation. Other questions are whether achieving a complete response (CR) is crucial, what initial therapy is best, whether and when autologous stem cell transplantation (ASCT) is needed, whether maintenance therapy is effective, and whether smoldering MM should be treated. The high cost of treatment has also become an important issue.

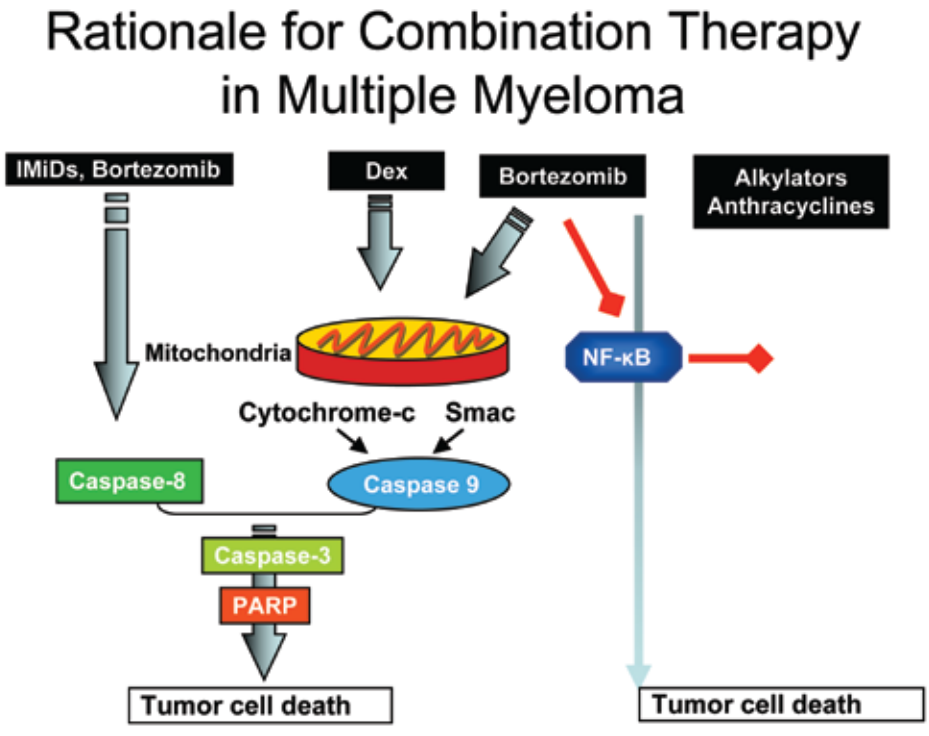
DIAGNOSIS AND INITIAL TREATMENT DECISIONS

The first question that must be answered when MM is diagnosed is whether the patient should begin treatment immediately. MM is preceded by the premalignant condition monoclonal gammopathy of undetermined significance (MGUS). Patients with MGUS are generally asymptomatic and are usually managed with a "watch and wait" approach. Cytogenetics plays a major role in MM risk stratification. In particular, patients with t(4;14) and the deletion 17p have a significantly worse prognosis, and those are the patients we tend to treat more aggressively. In addition, the International Staging System (ISS) is used in combination with cytogenetic markers because fairly significant differences in survival are associated with disease stage. For example, the overall survival of patients with t(4;14) and early stage disease is almost double that of patient with t(4;14) and ISS stage 3 disease [1].

The use of positron emission tomography (PET) scanning in MM patients to assess response to treatment is not new, but now it is recognized that PET scanning also has prognostic significance. In newly diagnosed untreated MM patients, positive results for F18-fluorodeoxyglucose PET scanning correlated with high-risk features; in particular, the number of focal lesions on PET scans independently correlated with inferior overall and event-free survival [2]. However, PET is not as effective for detecting disease in the spine and pelvis as magnetic resonance imaging, which when used in conjunction with PET can detect more than 90% of lesions in MM patients. Unfortunately, the high cost of PET scans can be problematic for patients.

NEW CHEMOTHERAPY REGIMENS

The aim of frontline therapy for MM is to substantially reduce the tumor burden. The degree of disease reduction is associated with improved outcome, including progression-free and overall survival. A regimen that will work quickly is important, and all of the new, novel agents can give high response rates. Different physicians use different



Rationale for the effectiveness of 3- and 4-drug combinations in the treatment of multiple myeloma (MM) patients. IMiDs indicates immunomodulatory drugs; Dex, dexamethasone; NF, nuclear factor; PARP, poly (ADP ribose) polymerase; Smac, second mitochondria–derived activator of caspases. Reproduced from [6] with permission of Expert Reviews Ltd.

approaches, and there is a rationale behind each approach.

Dexamethasone used to be the drug of choice for initial treatment of MM, but CR was rarely achieved with dexamethasone alone. Now, however, routine MM therapy for both newly diagnosed and relapsed/refractory disease includes the immunomodulators lenalidomide and the proteasome inhibitor bortezomib. Based on the results of phase III studies, bortezomib is approved for the treatment of MM, and lenalidomide plus dexamethasone is approved for relapsed MM following at least 1 prior therapy [3-5].

These agents in various combinations with chemotherapy are used both before and after ASCT and in patients who are ineligible for ASCT. With new combination therapies response rates have gone up 100%, and CR rates have also gone up, to approximately 40%.

High-dose chemotherapy supported by ASCT is a standard approach for MM patients who are <65 years old and without comorbidities. Recent clinical trials have demonstrated the effectiveness of 3- and 4-drug combinations incorporating novel agents before ASCT (Figure). The combination of lenalidomide, bortezomib, and dexamethasone in particular is highly effective for previously untreated MM and is the first regimen to result in a 100% response rate without ASCT. This regimen has shown very good tolerability over a lengthy treatment period, with manageable toxicities, and may represent the basis of future standards of care in previously untreated MM. In addition, trials are evaluating early versus delayed ASCT after induction with novel agents.

The use of thalidomide, lenalidomide, or bortezomib as maintenance therapy after transplantation also has shown promising results with improvements in progression free survival. Outcomes for the use of novel agents in elderly patients who are not eligible for ASCT are encouraging.

CONCLUSIONS

More promising therapies for MM are currently being investigated, so physicians should encourage patients to participate in clinical trials. Physicians must also keep in mind that with the many new and effective treatments, one size does not fit all. Patients must be carefully evaluated for risk factors and comorbidities before frontline therapy and monitored during treatment for adverse effects so that optimal results can be achieved.

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How I Treat Acute Myeloid Leukemia

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INTRODUCTION

Acute myeloid leukemia (AML) can be cured with current approaches in 30% to 40% of newly diagnosed younger patients, but the overall outcome has not improved in recent years. Although the rate of complete remission (CR) after induction chemotherapy has increased over the past 2 decades and postremission chemotherapy is routinely used, most patients suffer a relapse of AML and eventually die from the disease. Barriers to a higher cure rate for AML include drug-resistant disease and treatment toxicity. In particular, the outcome in adults older than 60 years remains poor, with <10% of patients who achieve remission remaining alive and disease free [1].

STEM CELLS IN ACUTE MYELOID LEUKEMIA

The importance of cancer stem cells was first recognized in AML. Although the morphology of the individual leukemia cells from a patient with AML appears the same, there is actually profound biologic heterogeneity. When cells from AML patients were separated according to antigenic expression and transplanted into mice, only the very immature progenitors produced AML and were therefore clonogenic. Importantly, this clonogenic ability was demonstrated in only ~0.3% of the cells [2]. Thus, even though many drugs we give to patients produce profound cytoreduction, there is a resistant sub-population of residual cells, probably enriched in stem cells, that persists and produces relapse.

Hematopoietic precursors are designed to survive repeated exposure to multiple types of natural toxins. Most resistance mechanisms have been shown to be amplified in undifferentiated precursors. Studies of marrow "purging" showed that normal stem cells can survive exposure to huge doses of chemotherapeutic agents in vitro. Therefore, it is not surprising that leukemia subtypes that are derived from hematopoietic stem cells, such as Philadelphia chromosome positive AML and leukemias evolving from MDS, are particularly resistant.

Gene expression studies that compared normal stem cells and AML stem cells were performed in the hope of finding a few different genes that could be targeted, but about 3000 genes had differential expression [3]. The mechanism(s) by which most mutations affect leukemogenesis, drug resistance, or drug sensitivity are unknown, and most are not "targetable," except perhaps indirectly, by epigenetic-modifying therapy.

HOW TO DEFINE ACUTE MYELOID LEUKEMIA

A recent World Health Organization (WHO) modification eliminated the RAEB-t (refractory anemia with excess blasts in transformation) group in myelodysplastic syndrome (MDS) and changed the criterion for the diagnosis of AML from ≥30% to >20% marrow blasts [4]. This change can make it difficult to compare more recent results with older studies and can result in a mixture of different "clinical phenotypes" of patients in current studies. For example, in many patients, AML is a rapidly proliferative disease with high white blood cell counts that requires prompt treatment, whereas what I have termed "WHO AML," potentially defined by 20.5% blasts with variably severe cytopenias, may not require immediate, aggressive treatment. The latter is probably indistinguishable biologically from MDS.

TREATMENT OF ACUTE MYELOID LEUKEMIA

The standard remission-induction regimen for patients with AML used by the Cancer and Leukemia Group B and others has been treatment with 7 days of cytarabine and 3 days of daunorubicin or other anthracyclines. Unfortunately, multiple attempts to improve upon the induction results of so-called "3 & 7" have not been successful. Multiple doses of cytarabine administered as a single agent at doses of 1500 to 3000 mg/m^2 for 2 to 4 courses as post-remission intensification has become the standard backbone of post-remission therapy for young and middle-aged adults with AML in first CR, but randomized trials have not shown an advantage for high-dose cytarabine consolidation for patients older than 60 years [1].

***THE* MAJOR ADVANCE IN AML THERAPY IN THE PAST 10-15 YEARS:**

ZOFRAN

AZOLES FOR PREVENTION/TREATMENT OF INFECTIONS WITH MOLDS

LEUCOCYTE DEPLETION TO PREVENT ALLOIMMUNIZATION

Improved survival with high-dose therapy in acute myeloid leukemia (AML) patients is largely attributable to better medications for supportive care.

The Importance of Better Supportive Care

Because of the risk of death from treatment-related toxicity, there is sometimes a reluctance to consider intensive induction therapy for older patients. A recent study in older adults from the Netherlands, however, demonstrated a 30-day mortality of only 10% and CR rates of almost 60%, even using higher does of daunorubicin [5]. This improved outcome is largely attributable to better supportive care, which arguably is the most important advance in AML treatment in the last 20 years (Figure). In the past, particularly in older patients, chemotherapy was extremely debilitating. Nausea and vomiting would frequently lead to erosion of the distal esophagus, serving as an entry point for systemic Candida infections. Esophagitis is now rare because of potent antiemetic drugs such as ondansetron. Patients remain nutritionally replete and can often go home on day 8 with a near normal performance status. Newer antifungal antibiotics have almost eliminated the use of amphotericin B and its adverse effects such as bone marrow suppression and kidney damage. Lastly, the incidence of alloimmunization and refractoriness to platelet transfusion has been substantially reduced with the use of leukoreduced blood products [6]. One cannot underestimate the profound effect these changes have had with resulting reduced morbidity and mortality, even in older patients.

Transplantation in Acute Myeloid Leukemia

Determination of the eligibility and advisability for transplantation is a very important aspect of the management of patients with AML. Most large randomized trials included patients with a wide range of AML subtypes and showed no advantage using allo- or autotransplantation as post-remission consolidation. More critical, however, is the question of whether allogeneic transplantation is of benefit to patients in specific risk groups defined by cytogenetic or molecular testing. There is a general consensus that transplantation should be offered to transplantation-eligible patients with higher risk cytogenetics while reserving transplantation to second remission for most patients with cytogenetically or molecularly favorable characteristics. Thus, recent data have shown no advantage from transplantation in patients whose AML was NPM1 (nucleophosmin-1) mutated but FLT3 negative [7]. The transplantation data are somewhat conflicting in patients with internal tandem duplications of FLT3, although our current policy is to offer allogeneic transplantation to such individuals. A number of new mutations have been described, and it is clear that there are interactions between different mutations, and the role of transplantation in these multiple subgroups remains to be determined [8].

THE FUTURE OF AML TREATMENT

Many new noncytotoxic therapies are now available, including angiogenesis inhibitors, tyrosine kinase inhibitors, FLT3 inhibitors, histone deacetylase inhibitors, modulators of apoptosis, and immunologic manipulations. A critical challenge is to develop methodology to rapidly and efficiently evaluate these new agents. Many cooperative groups have begun to focus on exploratory studies using a randomized Phase II design to identify approaches worthy of pursuing in larger and more costly Phase III trials.

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How I Treat Acute Lymphoblastic Leukemia in Adult Patients

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INTRODUCTION

Acute lymphoblastic leukemia (ALL) is much less common in adults than children. The cure rate of adult ALL is approximately 40%, only half that of childhood ALL, probably because of biologic differences in leukemogenesis between adult and childhood ALL [1]. Unlike some hematological malignancies, the treatment of ALL never involves a watch-and-wait period. The disease usually has rapid onset and progression, and patients are often hospitalized and begin treatment within a week of diagnosis. Thus, in addition to physical evaluation, pretreatment assessment includes getting to know issues the patients must address as they face this abrupt change in their life.

CLASSIFICATION OF ACUTE LYMPHOBLASTIC LEUKEMIA

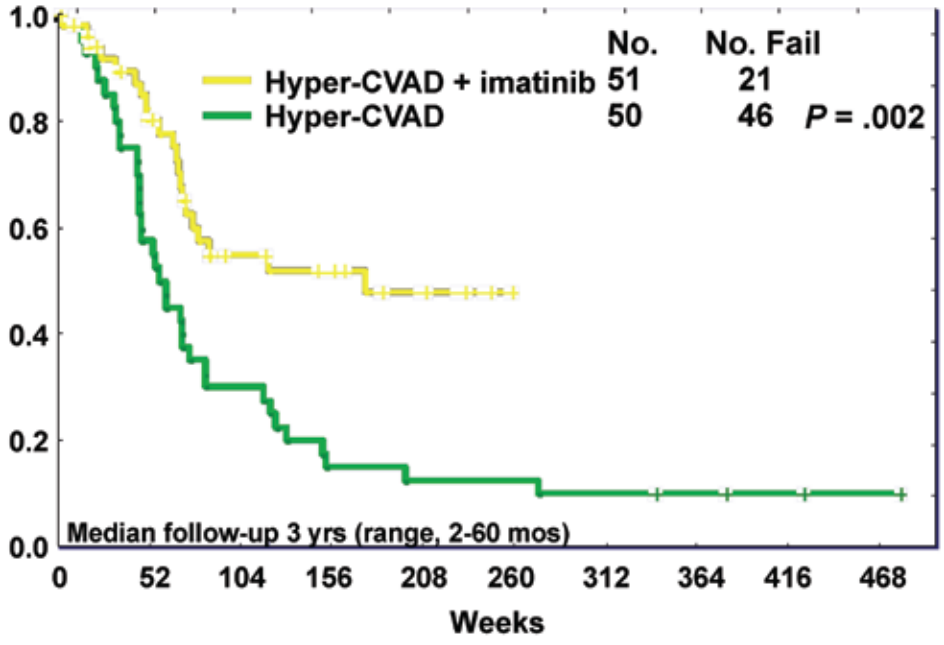
Pre–B-cell ALL is the most common form of adult ALL. These cells are CD19 positive and are the earliest lymphocyte in the ontogeny of B-cell development. Patients with T-cell ALL often have a mediastinal mass, and phenotypes differ depending on whether T-cell ontogeny is more mature or is pre–T-cell. B-cell ALL, in which the cells are more mature than in pre–B-cell ALL, is a different disease, a variation of Burkitt lymphoma that is now treated similarly to lymphoma rather than leukemia. In some cases, particularly in older patients, ALL with a CD19 positive–CD34 positive phenotype, may harbor the Philadelphia (Ph) chromosome, which has important features that affect prognosis and treatment.

TREATMENT OF ACUTE LYMPHOBLASTIC LEUKEMIA

During the initial examination, particular attention should be given to central nervous system (CNS)-related issues such as cranial nerve palsies. Testicles should be checked for masses. The usual laboratory work is performed, looking in particular for disseminated intravascular coagulation or for risks of tumor lysis syndrome indicated by high lactate dehydrogenase, phosphorous, and uric acid. Bone marrow aspiration and biopsy are performed and include analysis of morphology, phenotype, and cytogenetics. A chest x-ray is needed, as well as an echocardiogram in patients who will be treated with intensive anthracycline therapy. In many programs, HLA typing is performed upfront to assess transplantation possibilities and also so that HLA type can be used in selecting platelet products for patients refractory to random platelet transfusions.

With all forms of ALL there is a risk of CNS disease, and CNS prophylaxis is an important component of treatment. CNS prophylaxis procedures include lumbar puncture (LP) as part of the initial evaluation and during treatment and the use of drugs such as methotrexate. If LP results are positive, the patient should be treated during induction. If negative, CNS prophylaxis can be completed during consolidation.

The first step in treatment is induction therapy to achieve a complete remission (CR). If CR is rapidly attained and the patient has no risk factors, the protocol is continued. The complete remission rate in adults is 50% to 90%, depending on the age of the patient. Consolidation is followed by 1 to 3 years of some type of maintenance therapy. Approximately 35% of adult patients will be cured by this approach.



Increased survival of patients with Philadelphia chromosome–positive acute lymphoblastic leukemia (Ph+ALL) who received imatinib with induction chemotherapy compared with patients who did not. Hyper-CVAD indicates cyclophosphamide, vincristine, doxorubicin, dexamethasone, methotrexate, and cytarabine.

Options for induction therapy include a number of drug combinations that have been tested repeatedly in cooperative groups or single institutions. All of these regimens are built around the original pediatric regimen of vincristine and prednisone, with the addition of other agents such as anthracyclines in the Southwest Oncology Group (SWOG) protocol and cyclophosphamide in the Cancer and Leukemia Group B (CALB) protocol. Supportive care is important during induction and includes the prevention of infectious complications, particularly pneumocystis with Bactrim, Herpes simplex with acyclovir, and fungal infections, usually with fluconazole. Growth factors such as granulocyte colony-stimulating factor can be used to shorten the neutropenic phase.

An evaluation with repeated chromosome analysis should be performed at 4 weeks whether or not remission is achieved. Residual chromosome abnormalities during remission indicate that the remission is superficial and will not be long lasting.

Patients who do not achieve CR with induction therapy or who achieve CR after more than 2 cycles should undergo allogeneic transplantation. Ideally a donor should be found at the beginning of treatment to prepare for possible transplantation.

In patients in first relapse after remission, reinduction can be performed with the same drugs used for induction if the patient has been in remission longer than 18 months on maintenance. If it is a short remission and a donor is available, transplantation is the best option.

In ALL treatment the chemotherapy is frontloaded with the most effective drugs, so the disease at the time of relapse is usually highly resistant to therapy. Unfortunately, a limited number of new agents for ALL are available, and the CR rate is very low, particularly in patients who relapse while on therapy or within the first year of treatment. Sometimes entering an investigational trial is the best therapy and can become the bridge to allow a patient to go on to a more definitive therapy. Second remission in adult ALL patients is not as durable as it is sometimes is in pediatric patients, so adult patients who relapse and then go into remission should be treated with transplantation. Patients older than 50 years who are in remission have a poor prognosis, and in these cases reduced-intensity transplantation may preserve remission. Ongoing studies are investigating the use of minimal residual disease analysis to determine the optimal timing for transplantation [2]. Relapsed patients without a suitable donor should enter investigational clinical trials.

NEW AGENTS IN THE TREATMENT OF PH-POSITIVE ACUTE LYMPHOBLASTIC LEUKEMIA

Philadelphia Chromosome-positive (Ph+) is the one disease in ALL for which treatment has changed. The Ph-chromosome abnormality in ALL, which increases with age and is present in 35% to 40% of patients older than 60 years, has been considered a poor prognostic feature that should be treated with transplantation if possible. With a fully ablative allogeneic transplantation with radiation the cure rate is 50%. Now, however, the tyrosine kinase inhibitors such as imatinib or dasatinib can be administered during induction therapy without additional toxicity. The CR rates with the combination of chemotherapy and these drugs at our institution are 90%, and most of these patients are in a molecular remission at the end of induction (Figure). These drugs also seem to be useful both before and after transplantation [3].

CONCLUSIONS

Achieving a cure in adult ALL patients remains challenging. However, the dramatic improvement of the treatment of Ph-positive ALL with the use of tyrosine kinase inhibitors gives reason to hope for more dramatic improvements with the use of new treatment agents. Because new treatments, along with the optimization of existing treatments, are currently under investigation, participation in clinical trials is an option that may benefit current and future patients.

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How I Treat Myelodysplastic Syndromes

Presented by:

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INTRODUCTION

Ideally, therapy for patients with myelodysplastic syndromes (MDS) would be guided by pathophysiological understanding. Not only does targeted therapy not exist (except for rare cases of 5q-rearranged chronic myelomonocytic leukemia [CMML] responsive to imatinib), MDS is a very heterogeneous disease. MDS is a disease of older adults; the mean age is 68 to 70 years; therefore, comorbidity plays an important role in outcome. Disease heterogeneity dictates a therapeutic approach; more aggressive therapies are appropriate for patients with a worse prognosis, and a less aggressive approach is indicated for those with high-risk disease. It is important to consider allogeneic transplantation for higher risk patients earlier in the course of their disease.

THERAPEUTIC APPROACHES IN MDS

A general algorithm [1] for the treatment of MDS is presented in Figure 1. Some potential therapeutic modalities are described below.

1. Transplantation

A classic study by Cutler et al [2], which was done in the era before reduced-intensity conditioning transplantation, showed that patients with higher risk International Prognostic Scoring System (IPSS) disease were likely to live longer if allogeneic stem cell transplantation was applied at diagnosis. Patients with lower risk IPSS disease (low risk and intermediate-1) should have their transplantation delayed until their disease progresses, given the risk of the stem cell transplantation procedure. The advent of reduced intensity allogeneic stem cell transplantation allows those patients between ages 55 and 75 years to undergo stem cell transplantations that are associated with reasonable disease-related mortality but still with a significant relapse rate [3]. For patients with high-risk MDS, it is reasonable to consider a reduced intensity transplant to treat the disease but clear-cut data showing the benefit of this approach are lacking. Moreover, the value of cytoreduction prior to the stem cell procedure is unclear. Those that respond to 5-azacitidine will have a better outcome after stem cell transplantation than those who fail to respond, but this could represent identification of a more biologically responsive subgroup.

2. DNA Hypomethylating Agents

The most important class of therapeutic agents in MDS is the DNA hypomethylating agents, 5-azacitidine and decitabine. Both of these drugs are well tolerated at commonly used doses. They may work by allowing transcription of tumor suppressor genes repressed by promotor hypermethylation. Both 5-azacitidine and decitabine delay time to Acute Myeloid Leukemia (AML) transformation or death when compared to supportive care. A recent study in higher risk MDS patients that compared 5-azacitidine treatment to conventional care regimens (supportive care, AML induction, or low-dose cytarabine) demonstrated a 9-month median survival benefit for those randomized to azacitidine [4]. As such, azacitidine is the treatment of choice for higher risk MDS patients and also has utility in lower risk patients.

3. Growth Factors

Although the use of erythroid stimulating agents in a patient with solid tumors is controversial because of the potential promotion of cancer growth, such agents are deemed to be safe and potentially effective in those with myelodysplastic syndrome. Erythropoietin treatment as a single agent improves the hematocrit in approximately 50% of patients, especially those with lower baseline serum erythropoietin levels. Recent studies suggest that the use of erythropoietin in combination with granulocyte colony-stimulating factor (G-SCF) treatment can improve the hematocrit as well as overall survival [5].

4. Immunosuppression

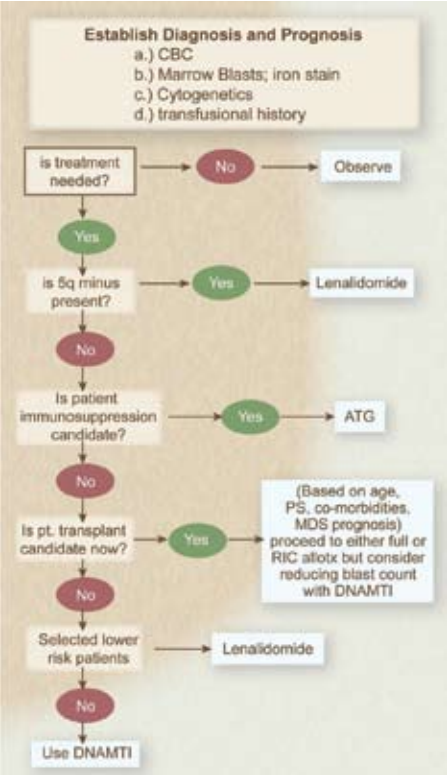
A subset of patients with MDS, particularly those with lower risk IPSS disease, may have a pathophysiology resembling that of aplastic anemia in which T-cell–mediated impairment of stem cell function occurs. It has been known for some time that some patients with MDS will respond to immunosuppressive therapy with prednisone or more potent approaches such as anti-thymocyte globulin with or without cyclosporine. Recently, responses have been demonstrated in selected MDS patients with the powerful immunosuppressant, the anti-CD52 agent alemtuzumab [6].

5. Lenalidomide

Lenalidomide, an immunomodulatory agent used extensively in the treatment of patients with multiple myeloma, has an important role in the management of patients with 5q– MDS. About two-thirds of patients with 5q– MDS (with or without other chromosomal abnormalities) will experience a transfusion-free period that may be durable in many cases [7]. The response rate in patients with non-5q MDS is considerably lower [8] and may be no higher than that seen with the hypomethylating agents.

6. Chelation Therapy

Many patients with MDS, particularly those with lower risk IPSS disease, have a high transfusional burden with an elevated serum ferritin and presumptive iron deposition in tissues such as skin, liver, and



General treatment algorithm for myelodysplastic syndrome (MDS). CBC indicates complete blood count; EPO, erythropoietin; Darbo, darbopoietin; G-CSF, granulocyte colony-stimulating factor; RARS, refractory anemia with ringed sideroblasts; ATG, antithymocyte globulin; PS, prognostic score; RIC, reduced-intensity conditioning; allotx, allogeneic transplantation; DNAMTI, DNA methyltransferase inhibitor [1]. Blood by AMERICAN SOCIETY OF HEMATOLOGY. Copyright 2010 by AMERICAN SOCIETY OF HEMATOLOGY (ASH). Reproduced with permission of AMERICAN SOCIETY OF HEMATOLOGY (ASH) in the format Journal via Copyright Clearance Center.

heart. High serum ferritin levels are correlated with poor outcome in MDS in general and particularly in MDS patients undergoing stem cell transplantation [9]. Moreover, it is possible to lower the iron burden with subcutaneous deferoxamine or with the more recently available oral iron chelator deferasirox. Whether or not such medication-induced lower iron burden and serum ferritin is associated with a beneficial outcome is unclear. Prospective randomized trials are required to show that iron chelation therapy, which can be toxic, expensive, and cumbersome, decreases the rate of adverse outcomes secondary to iron overload. For now, iron chelation therapy can be recommended cautiously in selected patients who are expected to live for at least several years and will require many red cell transfusions.

7. Targeted Therapy

The tyrosinse kinase inhibitor imatinib works well in those few patients with chronic monocytic leukemia in which there is an activation of platelet-derived growth factor beta due to a translocation involving the long arm of chromosome 5. In the last 2 years, a number of new mutations including those in c-cbl, TET2, ASXL-1 have provided the hope that targeted therapy will be possible in a larger subgroup of patients [10].

CONCLUSION

DNA hypomethylating agents in higher risk patients and lenalidomide and 5q– MDS represent therapeutic advances that lead to better long-term outcomes; nonetheless, there is a critical need for a greater understanding of pathophysiology at the molecular level. The current major strategy in therapeutic development in MDS is to combine hypomethylating agents with lenalidomide or with other epigenetic therapies such as histone deceatylase (HDAC) inhibitors. Randomized trials comparing hypomethylating agents alone to hypomethylating agents plus lenalidomide or HDAC inhibitors are underway or being developed.

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How I Treat Chronic Myeloid Leukemia

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INTRODUCTION

Although there are only approximately 2000 new cases of chronic myeloid leukemia (CML) in the United States per year, this disease has revealed much about the process of going from the bench to the bedside in cancer treatment. CML was the first disease for which a specific chromosomal abnormality was found to drive the disease, the Philadelphia chromosome; the first disease for which unique molecular tests were developed to monitor disease, by fluorescence in situ hybridization (FISH) and then by polymerase chain reaction (PCR); and one of the first leukemias for which transplantation became the standard of care. And now, CML is the first disease for which targeted tyrosine kinases or targeted molecules have been shown to have an impact. Because of our ability to monitor cases, to apply molecular biology to the disease through the use of tyrosine kinase small-molecule inhibitors, and to integrate these treatment innovations with transplantation, CML is a model of where we would like to be in the treatment of other cancers.

THE PHILADELPHIA CHROMOSOME

The Philadelphia (Ph) chromosome, a reciprocal translocation of chromosomes 9 and 22, was first described in 1960 as a shortened chromosome 22 present in myeloid cells from patients with CML (Figure) [1]. This was the first report of a human cancer associated with a specific genetic abnormality. Ninety-five percent of patients with CML have the Ph chromosome—hence, this chromosome is the hallmark of CML.

The Ph chromosome can be detected in bone marrow cells in metaphase by standard cytogenetic techniques. The Ph chromosome is present in all myeloid cell lineages, including erythrocytes, granulocytes, monocytes, and megakaryocytes, as well as some cells of lymphocytic lineage, indicating that malignant transformation to CML originates at the stem cell level.

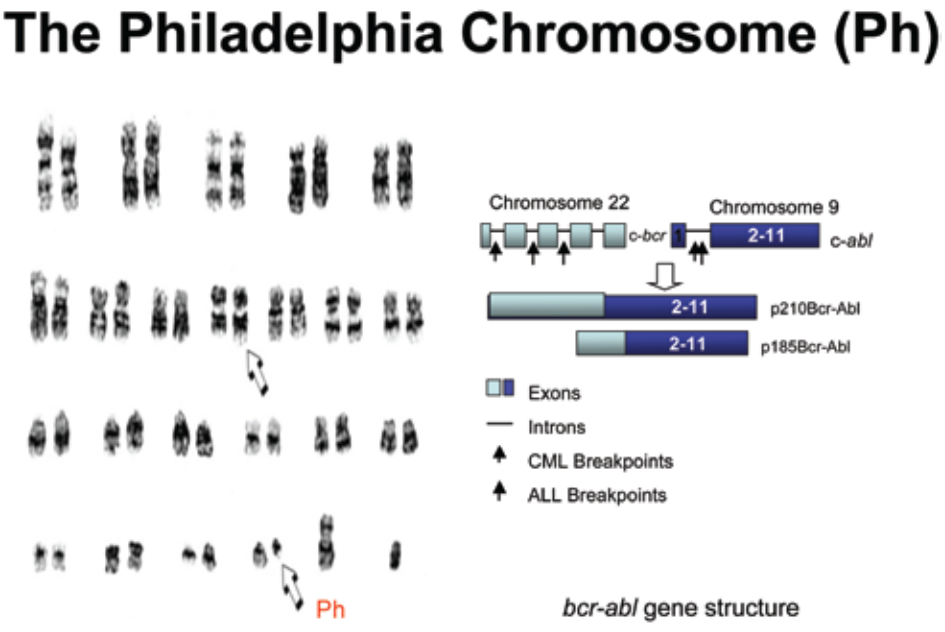
TYROSINE KINASE INHIBITION IN CHRONIC MYELOID LEUKEMIA

The Ph-chromosome translocation results in the oncogenic BCR-ABL gene fusion, which encodes the Bcr-abl fusion protein, a unique protein that drives the biology of CML. Usually there have to be multiple hits to cause a cancer, but CML is unique because in the chronic phase that single oncogene drives all of the functions leading to tumor development. Because the ABL gene expresses a membrane-associated protein, a tyrosine kinase, the BCR-ABL transcript is also translated into a tyrosine kinase. In chronic-phase CML, a unique drug, imatinib, which is a tyrosine kinase inhibitor (TKI), was found to make a huge impact through a single targeted molecule that blocks all those pathways and abnormalities so that normal cell behavior is restored. This is a dramatic example of how new drugs can make an impact in natural history of a disease.

Unfortunately, however, although imatinib is very effective for treatment of CML in the chronic phase, in the accelerated phase of blast crisis neither TKIs nor transplantation make an impact, and no effective treatments are available.

TREATMENT OF CHRONIC MYELOID LEUKEMIA

Targeted TKI therapy has quickly replaced transplantation as front-line therapy for chronic-phase CML. More than 90% of



The Philadelphia (Ph) chromosome, a reciprocal translocation of chromosomes 9 and 22, is the hallmark of chronic myeloid leukemia (CML).

patients in the chronic phase will obtain a hematologic remission; the majority of patients (80%) who are treated in the chronic phase achieve a complete cytogenetic remission, and those patients have an excellent survival rate (90%) [2].

A minority of patients with chronic-phase CML may demonstrate primary resistance to imatinib therapy, become resistant to therapy after an initial response, or progress to advanced-phase disease. In such cases, 2 second-generation targeted TKI drugs, dasatinib and nilotinib, may be effective. In addition to BCR-ABL, dasatinib hits multiple oncogenic tyrosine kinases that might be involved in disease evolution. Nilotinib is a "rationally designed" BCL-ABL inhibitor that was engineered according to the imatinib structure. In some cases BCL-ABL mutation analysis may be helpful in the selection of an optimal second-generation TKI [3].

Therapy with any modality is less successful for those patients in advanced-phase disease compared with chronic phase, so early detection of impending relapse and progression is an important aspect of treatment. Cytogenetic assessment should be performed by chromosome banding analysis of marrow cell metaphases until complete cytogenetic remission has been achieved and confirmed. Interphase FISH cannot be used to assess a less-than-complete response, but it can substitute for chromosome banding analysis to monitor the completeness of a complete cytogenetic remission, provided that BCR-ABL 1 extrasignal, dual color, dual fusion, or in situ hybridization probes are used and that at least 200 nuclei are scored. Disease staging before initiating therapy, including bone marrow analysis for morphology and cytogenetics, is also recommended. Early monitoring after starting imatinib therapy may also be useful in predicting response.

Despite the success of tyrosine kinase inhibitors, this treatment still fails in some patients. Patients with advanced disease tend to do better if they are treated with tyrosine kinase inhibitors before transplantation, but so far we have not made a difference in long-term survival in the accelerated phase with blast crisis with these drugs, even in combination regimens, so transplantation is the best option for these patients [4].

Can patients ever get off imatinib? Trials are underway to determine whether CML patients can safely discontinue imatinib. Results thus far indicate that approximately 40% of patients who discontinued the drug have stayed in complete molecular remission for 2 years, but the majority of them do not. These patients have restarted imatinib, and all of those people have gone back to responses [5]. The concern is that the usual CML time to progression from chronic to accelerated phase is about 3 or 4 years, and it is possible that every month that patients are off therapy the disease may be progressing. So unless there is a compelling reason that someone wants to get off the drug, such as if they want to become pregnant, this is clearly a clinical trial issue. Otherwise, physicians should keep patients on medication and encourage compliance.

THE FUTURE OF CHRONIC MYELOID LEUKEMIA TREATMENT

Second-generation TKIs may become the first-line therapy for CML, but they are more expensive that generic imatinib, and we don't know the long-term outcomes with these agents. Therefore, it would be useful to design trials to determine how to combine a generic drug with a second-generation drug, a trial in which patients start with the more important drug, and if they get a tremendous response, they go on maintenance with the less expensive drug.

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To assist us in evaluating the effectiveness of this activity and to make recommendations for future educational offerings, please take a few minutes to complete this evaluation form. ***You must complete this evaluation form to receive acknowledgment for completing this activity.***

Please answer the following questions by circling the appropriate rating:
5 = Outstanding 4 = Good 3 = Satisfactory 2 = Fair 1 = Poor

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Upon successful completion of this educational activity, participants should be better able to:

Evaluate the new molecular and immunologic treatment being developed for hematologic malignancies	1	2	3	4	5
Demonstrate the rationale for new targeted diagnostic and evolving therapeutic strategies used in the care of patients with lymphoma, myeloma, acute and chronic leukemia, and myelodysplasia	1	2	3	4	5
Interpret the role and timing of hematopoietic cell transplantation in the management of younger and older patients' hematologic malignancies	1	2	3	4	5
Summarize the evolving therapeutic strategies in the treatment of hematologic malignancies	1	2	3	4	5

Overall Effectiveness of the Activity

Was timely and will influence how I practice	1	2	3	4	5
Will assist me in improving patient care	1	2	3	4	5
Fulfilled my educational needs	1	2	3	4	5
Avoided commercial bias or influence	1	2	3	4	5

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❒ Reinforced my current practice/treatment habits
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❒ Enhanced my current knowledge base

Will the information presented cause you to make any changes in your practice? ❒ Yes ❒ No
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5.	A	B	C	D
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7.	A	B	C	D
8.	A	B	C	D
9.	A	B	C	D
10.	A	B	C	D

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1. **Which of the following statements is true regarding current treatment of follicular lymphoma (FL)?**
   A. FL is frequently misdiagnosed.
   B. Rituximab treatment for FL has resulted in improved survival.
   C. Rituximab should not be combined with chemotherapy drugs.
   D. All of the above.

2. **Which of the following statements is true regarding current treatment of diffuse large B-cell lymphoma (DLBCL)?**
   A. Rituximab is not very effective as a single agent for DLBCL but is very effective when combined with existing chemotherapy regimens.
   B. Cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) is not an effective treatment for DLBCL.
   C. Patients older than 60 years should not be treated with rituximab.
   D. None of the above.

3. **Which of the following statements is true regarding current treatment of peripheral T-cell lymphoma (PTCL)?**
   A. PTCL is a group of diseases with similar characteristics and treatments.
   B. The antifolate pralatrexate is the only agent that is currently FDA approved for the treatment of relapsed PTCL.
   C. PTCL patients most often present with early stage disease.
   D. All of the above.

4. **Which of the following statements is true regarding current treatment of cutaneous T-cell lymphoma (CTCL)?**
   A. Initiating therapy with sequential palliative treatment rather than aggressive therapy may be appropriate even for patients with advanced-stage disease.
   B. Intense pruritis in CTCL patients may not be relieved by standard antiitching medications.
   C. Interferon is an active drug in the treatment of CTCL.
   D. All of the above.

5. **Which of the following statements is true regarding current treatment of Hodgkin's lymphoma (HL)?**
   A. The International Prognostic Score is always a more accurate prognostic indicator than positron emission tomography (PET) scanning.
   B. Adriamycin (doxorubicin), bleomycin, vinblastine, dacarbazine (ABVD) has been replaced by chemotherapy regimens that are obviously superior.
   C. Most HL patients are young, so preserving fertility should be addressed in patient counseling and choice of treatment.
   D. All of the above.

6. **Which of the following statements is true regarding current treatment of multiple myeloma (MM)?**
   A. With new combination drug therapies, response rates in MM have gone up 100%.
   B. Cytogenetics plays a major role in MM risk stratification.
   C. Routine MM therapy for both newly diagnosed and relapsed/refractory disease includes the immunomodulators thalidomide and lenalidomide and the proteasome inhibitor bortezomib.
   D. All of the above.

7. **Which of the following statements is true regarding current treatment of acute myeloid leukemia (AML)?**
   A. Drug-resistant disease is not a problem in AML.
   B. Supportive care of AML patients has improved little in the past 2 decades.
   C. A study demonstrated that because of treatment-related toxicity, adults older than 60 years should not be treated with high-dose chemotherapy, even though it is more effective.
   D. None of the above.

8. **Which of the following statements is true regarding current treatment of acute lymphoblastic leukemia (ALL)?**
   A. Treatment of ALL is more effective in adults than children.
   B. A "watch and wait" approach may be used in ALL treatment.
   C. Central nervous system prophylaxis is an important component of treatment in all ALL patients.
   D. All of the above.

9. **Which of the following statements is true regarding current treatment of myelodysplastic syndromes (MDS)?**
   A. Lenalidomide is approved for use in patients with 5q-minus MDS.
   B. Patients with lower risk disease benefit from transplantation performed as quickly as possible.
   C. Treatments for MDS are based on our complete understanding of disease pathophysiology.
   D. All of the above.

10. **Which of the following statements is correct regarding the treatment of chronic myeloid leukemia (CML)?**
    A. Current study results have confirmed that patients who have been in complete remission for 2 years or more on imatinib can safely discontinue the drug.
    B. Imatinib treatment is highly effective in all phases of CML.
    C. With targeted tyrosine kinase inhibitor therapy, the majority of patients treated in chronic phase CML achieve a complete cytogenetic remission.
    D. None of the above.

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