Blood and Marrow TRANSPLANTATION

REVIEWS

A Publication of the American Society for Blood and Marrow Transplantation

Issues in Hematology, Oncology, and Immunology VOLUME 18 NO 2 2008

IN THIS ISSUE

This publication is supported by an educational grant from

MILLENNIUM

Treatment Advances for Multiple Myeloma and Mantle Cell Lymphoma: The Changing Landscape

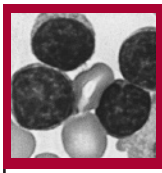
John Wingard and Baldeep Wirk

The management of multiple myeloma has changed dramatically over the past 2 decades. Testing of new treatment options continues at a rapid pace. The advances have resulted in improved survival rates not only in clinical trial participants, but these benefits have been applied to general practice and survival rates are improving in population-based studies as well. Although cure largely remains beyond a realistic prospect, durable control of disease is achievable in the majority of patients. Multiple myeloma is characterized by clinical heterogeneity based largely on genetics; therefore, a risk adapted strategy may be helpful in guiding therapeutic decisions. More progress is needed and many questions remain about how to choose between the various current and emerging treatment options in clinical practice. Such issues are being addressed in current and planned future studies: what are the best first-line and salvage treatment options and what options should be considered for various subgroups of patients, including the elderly, those with renal dysfunction, and those with certain comorbid medical conditions, such as peripheral neuropathy. Toxicities remain a challenge and occur with regularity in many of the treatment regimens. As multiple myeloma emerges as more of a chronic disease, considerable attention is being given to how we can best minimize toxicities with these regimens and thereby improve the quality of life.

Progress has also occurred with mantle cell lymphoma but at a much slower pace. Improved understanding about the heterogeneity of clinical behavior is perhaps one of the most important insights, some cases assuming an indolent course, other cases taking a much more aggressive course. Several case series suggest intensive treatment regimens that include stem cell transplantation may be helpful. Novel regimens including rituximab, bortezomib, and bendamustine have offered new hope to patients with this challenging subtype of non-Hodgkin lymphoma. How to select the optimal therapy for individual patients eludes us at present, but studies continue with the hope of significantly impacting the natural history of mantle cell lymphoma.

This issue contains extracts of a satellite symposium held at the 2008 BMT Tandem Meetings in San Diego, CA. Dr. Robert Rifkin discusses data presented at the 2007 American Society of Hematology meeting describing new treatment options for both multiple myeloma and mantle cell lymphoma. Dr. David Vesole focuses on concerns about toxicities of various treatment options for multiple myeloma. Dr. Christopher Flowers addresses first-line and salvage treatment options for mantle cell lymphoma and the role of HCT.

The fact that the first treatment decision can truly influence the ultimate disease outcome gives great impetus to determining how best to position the exciting new treatment options for individual patients. Hopefully, the needed answers will be forthcoming in future studies.



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Publishing and Production Services
CJP Medical Communications, a division of Carden Jennings Publishing Co., Ltd.

Blood and Marrow Transplantation Reviews is published by CJP Medical Communications.
375 Greenbrier Dr., Suite 100, Charlottesville, VA 22901
phone (434) 817-2000; fax (434) 817-2020

This publication is supported by an educational grant from Millennium Pharmaceuticals

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Guidelines Help Physicians Determine Optimal Time to Refer for BMT Consultation

The National Marrow Donor Program (NMDP) has a wealth of information on when to refer for possible blood stem cell transplant—guidelines that can be helpful to hematologists, oncologists, and other medical specialists.

The NMDP's Web presentation includes detailed information about disease treatments, outcomes, the transplant process, and referral timing.

The use of hematopoietic cell transplantation has grown over the past decade to become a standard of care for some diseases and a treatment option for others. The NMDP Web presentation lists:

- Diseases treatable by hematopoietic cell transplant
- Changing trends in diseases and patients treated

When transplant is indicated, the likelihood of a successful outcome can be improved if the transplant is performed at the most beneficial time in the course of the patient's disease. Links on the NMDP Web pages lead to:

- Guidelines on recommended timing for consultation
- Transplant outcomes by disease and disease stage
- Planning for transplant

An efficient patient referral process enables timely evaluation at a transplant center and coordination of patient care before, during, and after transplant.

To access the NMDP information for physicians on referral, browse to www.marrow.org/PHYSICIAN. Click on "When To Transplant" in the pull-down menu labeled "Physicians."

16 Young Clinicians, Investigators Selected for ASBMT Clinical Research Training Course

Sixteen young clinicians and investigators have been selected to participate in the second annual ASBMT Transplant Clinical Research Training Course from July 30 to Aug. 4 in Park City, Utah.

The five-day course assists fellows and young faculty in career paths toward successful clinical research in blood and marrow transplantation. The participants were selected competitively from among submitted applications, each including a proposed research project.

Major funding for the clinical research training course is being provided by Amgen, Histogenetics, Merck and Otsuka Pharmaceuticals and THERAKOS.

The selected scholars are:

- Jeffery Auletta, MD, Case Western Reserve University, Rainbow Babies and Children's Hospital, Cleveland, Ohio
- Jonathan Benjamin, MD, PhD, Stanford University Medical Center
- Christina Castilla-Llorente, MD, PhD, Fred Hutchinson Cancer Research Center
- William Clark, MD, MS, Vanderbilt University
- Sung Choi, MD, University of Michigan Cancer Center
- Luciano Costa, MD, PhD, Medical University of South Carolina
- David Delgado, MD, University of Wisconsin Children's Hospital
- Christine Duncan, MD, Dana-Farber Cancer Institute
- Hong Liu, MD, PhD, University of Florida Shands Cancer Center
- Chrystal Louis, MD, MPH, Baylor College of Medicine
- Taiga Nishihori, MD, Yale University School of Medicine
- Iskra Pusic, MD, Washington University School of Medicine
- Jessica Shafer, MD, Baylor College of Medicine
- Sophie Stein, MD, University of Pennsylvania
- Jonathan Storey, MD, Wake Forest Comprehensive Cancer Center
- Jeffrey Venstrom, MD, Memorial Sloan-Kettering Cancer Center

The course directors are Daniel Weisdorf, MD, of the University of Minnesota, and Nelson Chao, MD, of Duke University. They, together with nine other faculty members, are leading the sessions, as well as sharing their career stories and counsel. Free time for rest, recreation, and creative thinking is built into the schedule.

Lifetime Achievement Award Presented to Rainer Storb

The 2008 recipient of the ASBMT Lifetime Achievement Award is Rainer Storb, MD, head of the transplant biology program at the Fred Hutchinson Cancer Research Center, Seattle.

Dr. Storb has pioneered less toxic forms of allogeneic marrow and blood stem cell transplants for malignant and non-malignant blood diseases. The award, presented at the BMT Tandem Meetings, is supported by Pfizer, Inc.

Two New Investigators Win BBMT Editorial Awards

Two medical scientists are the recipients of editorial awards for new investigators for their articles published this past year in *Biology of Blood and Marrow Transplantation*.

Each award is accompanied by a $5,000 prize.

Robert Zeiser, MD, of Stanford University, is winner of the Ernest McCulloch & James Till Award for best basic science article by a new investigator. The award is supported by an education grant from StemCell Technologies Inc.

His article, published in the December 2007 issue, was "Host-Derived Interleukin-18 Differentially Impacts Regulatory and Conventional T Cell Expansion During Acute Graft-versus-Host Disease."

Kenneth Micklethwaite, PhD, of Westmead Millennium Institute, University of Sydney at Westmead Hospital, Sydney, Australia, is recipient of the George Santos Award for best clinical science article by a new investigator. The award is supported by an education grant from StemSoft Software Inc.

His article published in the June 2007 issue was "Ex Vivo Expansion and Prophylactic Infusion of CMV-pp65 Peptide-Specific Cytotoxic T-Lymphocytes following Allogeneic Hematopoietic Stem Cell Transplantation."

Selection of the winning articles was by the *BBMT* Editorial Board and the ASBMT Publications Committee. The awards were presented at the 2008 BMT Tandem Meetings in San Diego.

ASBMT

Symposium Report

Blood and Marrow TRANSPLANTATION REVIEWS

Front Line Therapy For Multiple Myeloma And Mantle Cell Lymphoma: The Role of Hematopoietic Cell Transplantation and Proteasome Inhibition Therapies

Release Date: June 30, 2008
Expiration Date: June 30, 2009.

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Overview

This publication will use a combination of didactic presentations of data in conjunction with patient case scenarios to elicit the most interactive discussion and learning environment. World-renowned thought leaders will discuss patient case scenarios and data supporting various treatment strategies for Multiple Myeloma (MM) and Mantle Cell Lymphoma (MCL), with the goal of defining front-line therapies for improving patient outcomes.

Target Audience

This activity is targeted to healthcare professionals who diagnose, manage, and treat patients with hematologic malignancies.

Learning Objectives

- Describe the current state-of-the-art front-line strategies for the treatment of multiple myeloma (MM) and mantle cell lymphoma (MCL).
- Identify clinical controversies in the management of MM and MCL.
- Summarize available research data on emerging treatments for MCL, including mono- and combination therapy with targeted agents, such as proteasome inhibitors, new cytotoxics, monoclonal antibodies, and autologous stem cell transplantation.
- Discuss the clinical implications of evolving therapies for MCL and directions for future research.
- Formulate treatment decisions based on supportive data presented.

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This material has been prepared based on a review of multiple sources of information, but it is not exhaustive of the subject matter. Participants are advised to critically appraise the information presented, and are encouraged to consult the above-mentioned resources as well as available literature on any product or device mentioned in this program.

Disclosure of Unlabeled Uses

This educational activity may contain discussion of published and/or investigational uses of agents that are not indicated by the FDA. The opinions expressed in the educational activity are those of the faculty and do not necessarily represent the views of the Medical College of Wisconsin, Carden Jennings Pharmaceuticals, or Millennium Pharmaceuticals.

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:

Robert M. Rifkin, MD: is a member of the speaker's bureau for Millennium and Celgene.

David H. Vesole, MD, PhD: is a member of the speaker's bureau for Celgene, Millennium, and Ortho Biotech.

Christopher R. Flowers, MD: has received research support from Biovest, Bayer, Johnson & Johnson, and Millennium, and he is an unpaid member of the Advisory Board for Biogen IDEC and Genentech.

Introduction

Major advances are changing the clinical management of hematologic malignancies. Within the past 5 years, four novel agents—thalidomide, lenalidomide, bortezomib, and pegylated liposomal doxorubicin—have been granted approval by the Food & Drug Administration (FDA) for treatment in multiple myeloma (MM). Presently, these agents are being evaluated for the front-line management of MM. Thalidomide and lenalidomide, along with bendamustine, are also being evaluated for the management of mantle cell lymphoma (MCL). Bortezomib, newly approved as salvage therapy in MCL, may also play a future role in the treatment of newly diagnosed patients. Given the importance of initial treatment choices on long-term clinical outcomes—as well as on subsequent treatment options—selecting the optimal first-line approach for patients with newly diagnosed MM or MCL is a critical step in improving patient outcomes and quality of life.

I. Upfront Combination Therapies: Multiple Myeloma and Mantle Cell Lymphoma

Robert M. Rifkin, MD, FACP

Several major abstracts on the treatment of newly diagnosed MM and MCL were presented at the 2007 American Society of Hematology (ASH) annual meeting in Atlanta, Georgia (Table 1). Among presentations focused on first-line treatment of MM, three phase II and III trials included patients who were candidates for transplant, and one phase III restricted enrollment to patients who were not eligible for transplantation. The phase II and III trials within the MCL population included patients with both indolent and aggressive variants of the disease.

Previously Untreated Myeloma

Bortezomib, thalidomide, dexamethasone (BTD) versus thalidomide and dexamethasone (TD)

The randomized, phase III, multicenter Italian Myeloma Network (GIMEMA) trial compared bortezomib, thalidomide, dexamethasone (BTD) with thalidomide, dexamethasone (TD) prior to transplant in newly diagnosed myeloma patients.[1] In the trial, 234 patients received three 21-day courses of induction therapy. Of these, 187 patients were evaluable for response to induction therapy and adverse events.[1]

Induction therapy included bortezomib 1.3 mg/m^2 on days 1, 4, 8, and 11, plus dexamethasone 40 mg on each day of and after bortezomib administration, and thalidomide 200 mg/d on days 1 to 63 (n = 92) in the BTD group. In the TD group, patients received dexamethasone 40 mg/d on days 1-4 and 9-12 of every 21-d cycle and thalidomide 200 mg/d from day 1 to 63 (n = 95). The primary endpoint was complete response (CR)—including immunofixation-negative CR and immunofixation-positive, near CR (nCR)—to induction therapy. Cavo and colleagues also evaluated response to first PBSCT in a subgroup of patients who had longer follow-up data available.[1]

One year after study initiation, the CR rate was higher in the BTD arm (38%) compared with the TD arm (7%; $P < .001$). In addition, more patients in the BTD arm than the TD arm achieved at least a very good partial response (60% versus. 25%; $P < .001$). Importantly, responses to induction therapy were maintained in the presence of the genetic abnormalities traditionally linked to poor prognosis.[1]

Peripheral blood progenitor cell (PBPC) harvesting was not adversely affected by the addition of bortezomib to thalidomide and dexamethasone. In the subgroup of patients where PBSC transplant (PBPCT) data were available, induction therapy with BTD compared with TD was associated with higher rates of CR ($P = .02$) and CR/nCR ($P = .05$) after first autologous transplantation with MEL-200.[1]

Addition of bortezomib to TD did not appear to increase toxicity, as most grade ≥ 2 and grade ≥ 3 adverse events were similar in the two treatment groups. However, some adverse events were more common in the BTD than in the TD group, including grade ≥ 3 skin rash (6.5% versus. 1%; $P = .04$) and grade 3 peripheral neuropathy (8% versus. 2%; $P = .07$). No deaths occurred during the induction phase, and one patient in each treatment arm discontinued therapy due to adverse events.[1]

In summary, preliminary findings from the phase III GIMEMA trial suggest that BTD is highly active and well tolerated in patients with newly diagnosed MM. Compared with TD, induction therapy with BTD leads to higher rates of CR and CR+nCR both before and after PBSCT. These outcomes are felt to have prognostic importance in this patient population.[1]

ECOG-E4A03: Lenalidomide with high-dose (RD) versus low-dose dexamethasone (Rd)

In the phase III Eastern Cooperative Oncology Group (ECOG)-E4A03 trial, Rajkumar and colleagues compared two lenalidomide/dexamethasone combinations—lenalidomide plus standard, high-dose dexamethasone (RD) or lenalidomide plus low-dose dexamethasone (Rd)—in 445 patients with newly diagnosed MM. The trial was designed to address both concerns regarding the adverse event profile of high-dose dexamethasone. In

Table 1. American Society of Hematology (ASH) 2007 annual meeting update

Previously Untreated Multiple Myeloma

Author	Phase	Regimen	No. patients	Response rate (% ≥VGPR)	Transplant candidate
Cavo[1]	III	BDT versus DT	256	60 versus 27	Yes
Rajkumar[2]	III	Rd versus RD	445	80 versus 67	Yes
Richardson[3]	I/II	BDR	53	52	Yes
San Miguel]4\	III	BMP versus MP	682	82 versus 50	No

Previously Untreated Mantle Cell Lymphoma

Author	Phase	Regimen	No. patients	Response rate (% overall)	Study Population
Rummel[5]	III	R-B versus CHOP	315*	93 versus 93	Indolent/Mantle
Epner[7]	II	R-HyperCVAD	49	88	Mantle
Geisler[8]	II	R-MaxiCHOP R-HiDAC	160	96	Mantle

*Interim analysis. B indicated bortezomib; CHOP, cyclophosphamide, doxorubicin, vincristine, andpredisone; D, high-dose dexamethasone; d, low-dose dexamethasone; M, melphalan; R, lenalidomide; R-B, rituximab + bendamustine; R-HiDAC, ritiximab + high-dose AraC; R-HyperCVAD, rituximab + fractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone; R-MaxiCHOP, ritiximab + dose-intensified CHOP; T, thalidomide.

particular, ECOG-E4A03 was designed to characterize the balance between the activity and toxicity of different dexamethasone regimens.[2]

All patients received lenalidomide 25 mg/day on days 1-21 every 28 days. Patients who were randomly assigned to the RD group (n = 223) also received dexamethasone 40 mg on days 1-4, 9-12, and 17-20 every 28 days, whereas those assigned to the Rd group (n = 222) received dexamethasone 40 mg days 1, 8, 15, and 22 every 28 days. The primary endpoint was response rate at 4 months.

As expected, several adverse events were significantly higher in the RD group than in the Rd group, including grade ≥3 infections (16% versus 6%; $P < .001$) and deep vein thrombosis/pulmonary embolism (DVT/PE) (25% versus 9%; $P < .001$). Indeed, patients in the RD group had higher rates of any grade ≥3 non-hematological adverse events (49% versus. 32%; $P < .001$) and any grade ≥4 non-hematological adverse event (20% versus. 9%; $P < .001$).

The overall response rate (ORR) was superior in the RD group when compared with the Rd group (82% versus 70%). Despite this finding, overall survival was higher in the low-dose group compared with the high-dose dexamethasone group ($P < .001$). The survival advantage of Rd over RD is apparent at one year (96% versus 87%) and 18 months (91% versus 80%). Upon closer analysis of the causes of death in each treatment group, Rajkumar and colleagues found that both disease progression and toxicity contributed to the excess mortality observed in the RD group.

Findings from ECOG-E4A03 have profound implications on the treatment of newly diagnosed MM. Contemporary trials now incorporate low-dose dexamethasone, rather than the higher-dose regimen, into their treatment protocols.

Bortezomib, lenalidomide, and dexamethasone

The final notable trial among patients with newly diagnosed, transplant-eligible MM presented at ASH focused on first-line therapy with bortezomib, lenalidomide, and dexamethasone. The phase I/II open-label study was designed to determine the maximum-tolerated dose (MTD), safety, and efficacy of the three-agent combination.[3]

Eligible patients could not have had any previous systemic therapy for MM, with the exception of treatment with bisphosphonates. Prior radiotherapy was permitted, but must have been completed at least two weeks before study entry. Among the 33 patients enrolled in the early portion of the study, demographics included: median age of 56 years; 84% had IgG MM; and, 47% had International staging system (ISS) Stage II/III disease.

For the phase I evaluation, patients were treated to the MTD of each of the following agents for up to eight 21-day cycles:

- Bortezomib IV 1.0-1.3 mg/m^2 on days 1, 4, 8, 11, 22
- Lenalidomide 15-25 mg on days 1-14
- Dexamethasone 20 mg/d on days 1, 2, 4, 5, 8, 9, 11, 12

In the original protocol, dexamethasone was started at a dose of 40 mg/d for the first four cycles. However, after an initial safety analysis found that dexamethasone 40 mg/d was not well tolerated beyond the first cycle, the starting dose was reduced to 20 mg/d. With this modified regimen, toxicities associated with the bortezomib, lenalidomide, and dexamethasone regimen were manageable. One patient developed grade 4 thrombocytopenia, and another developed DVT, which was treated with low molecular weight heparin (LMWH).[3]

Among 28 evaluable patients, the response rate was 89%, including CR, nCR, or very good PR (VGPR). All responding patients but one remain in remission, and two have proceeded to autologous stem cell transplantation (ASCT). After a mean follow-up of four months, the median time to progression (TTP), progression-free survival (PFS), and overall survival (OS) were not reached.[3]

Results of the phase I component demonstrate that the maximum planned dose of

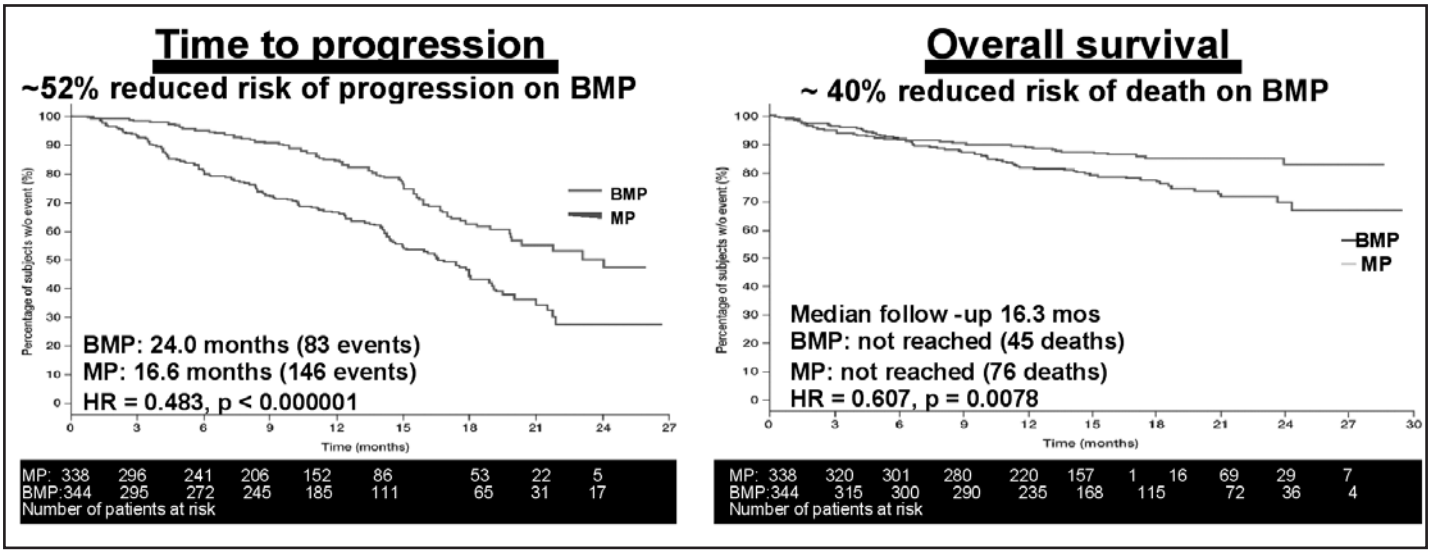

Figure 1. MMY-3002: BMP versus MP in newly diagnosed multiple myeloma. BMP indicates bortezomib, melphalan, and prednisone; MP, melphalan and prednisone. San Miguel, JF, Schlag R, Khuageva N, et al. MMY-3002: A phase 3 study comparing bortezomib melphalan prednisone (BMP) with melphalan prednisone (MP) in newly diagnosed multiple myeloma. Abstract presented at: 49th Annual Meeting of the American Society of Hematology. 2007; Atlanta, GA. Abstract 76.

lenalidomide 25 mg, bortezomib 1.3 mg/m^2, and dexamethasone 20 mg. Accordingly, the phase II enrollment is moving forward with this regimen, with 55 patients enrolled to date. In addition, the bortezomib, lenalidomide, and dexamethasone regimen forms the basis of therapy in another ongoing trial, which is evaluating whether adding oral cyclophosphamide can improve on these preliminary results. Updated results of this important trial will be presented at upcoming national meetings.

VISTA: Melphalan and prednisone (MP) versus MP plus bortezomib (MPV)

The final noteworthy ASH abstract in MM evaluated first-line therapy in a different patient population: older patients (>65 years) who were not eligible for stem cell transplantation. In the phase III VISTA trial, 682 patients were randomly assigned to treatment with bortezomib, melphalan, and prednisone (BMP) or melphalan and prednisone (MP) alone.[4]

Patients in the BMP group received treatment with bortezomib 1.3mg/m^2 twice weekly (weeks 1, 2, 4, 5) for four 6-week cycles, followed by once weekly (weeks 1, 2, 4, 5) for five 6-week cycles, as well as oral melphalan 9mg/m^2 and prednisone 60mg/m^2 once daily on days 1-4 of each cycle. Patients in the MP group received nine 6-week cycles of the same doses of once daily melphalan and prednisone on days 1-4. All patients continued therapy until disease progression, unacceptable toxicity, or for a total of nine cycles (54 weeks). The primary endpoint was TTP.

The pre-treatment characteristics of patients in the vista trial are representative of a high-risk advanced-disease population. The median age was 71 years, and 30% of patients were older than 75 years. The majority of patients (63%) had IgG myeloma, 34% had KPS ≤70%, 27% had bone involvement with >10 lytic bone lesions, 33% had beta$_2$-microglobulin >5.5mg/L, and 60% had albumin <35g/L.

The trial was stopped early at a planned interim analysis due to a significant survival advantage with triple-agent therapy (Figure 1). After 16.3 months of follow-up, median OS was not reached in either arm. However, with 76 deaths in the MP arm and 45 deaths in the BMP arm, treatment with BMP reduced the risk of death by 40% (HR, 0.607; P = .0078). The addition of bortezomib to melphalan and prednisone also delayed the median time to progression from 16.6 months in the MP arm to 24.0 months in the BMP arm, resulting in a 52% reduction in the risk of TTP (HR, 0.483; P < .000001).

Compared with MP alone, the addition of bortezomib did not appear to increase toxicity. The rates of discontinuation due to adverse events were similar in the BMP and MP groups. Given comparable toxicity profiles, longer time to next therapy with BMP may be an indicator of a superior quality of life.[4]

Previously Untreated Mantle Cell Lymphoma

Rituximab/Bendamustine versus R-CHOP

The first interim analysis of a multicenter phase III trial from the Study Group Indolent Lymphomas, Germany (StiL), suggested similar efficacy and lower toxicity with rituximab combined with bendamustine (R-B) when compared to cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP).[5]

In the trial, 439 patients with follicular (52%), indolent (28%) or mantle cell (20%) lymphomas were randomly assigned to treatment with rituximab 375 mg/m^2 on day 1 plus either bendamustine 90 mg/qm on days 1 and 2 every 28 days or standard CHOP therapy every 21 days for a maximum of 6 cycles. A total of 273 patients were evaluable, including 139 in the R-B group and 134 in the R-CHOP group. The primary endpoint was event-free survival (EFS).

Patients in the R-B and R-CHOP groups had similar response rates, including ORR (94% versus 93%) and CR (51% versus 40%). After a median follow-up of 17 months, seven deaths have been reported in the R-B group, compared with eight deaths in the R-CHOP group. In addition, progressive or relapsed disease has been reported in 27 and 32 patients in the R-B and R-CHOP groups, respectively.

Although the response rates are similar, the toxicity profiles associated with R-B and R-CHOP have notable differences. Patients in the R-B group were less likely than those in the R-CHOP group to report total alopecia (0% versus 40%), infectious complications (19 patients versus 41 patients), or grade 3-4 leukocytopenia (12% versus 41%).

In summary, the StiL investigators demonstrated a tendency toward lower toxicity with B-R compared with R-CHOP.[5] The final analysis of this trial, with a longer observation period, may further distinguish the efficacy and safety outcomes of these treatment options. In addition, a future trial to evaluate R-B as long-term maintenance in follicular lymphoma is being planned.

SWOG-0213: R-HyperCVAD

A phase II SWOG-0213 trial was designed to validate a single-institution protocol across several institutions.[6, 7] The original protocol, developed at the MD Anderson Cancer Center (MDACC) in Houston, Texas, includes treatment with rituximab plus fractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone (R-HyperCVAD) alternating every 21 days with rituximab plus high-dose methotrexate-cytarabine (Ara-C) for a total of eight cycles.[6] At MDACC, Romaguera and colleagues found a 97% response rate, a 87% CR rate, and a 3-year failure-free survival rate of 73% among 97 patients with newly diagnosed MCL.[6]

In SWOG-0213, 49 patients were treated with the HyperCVAD protocol, and 40 patients were evaluable for response. The ORR was 88%, including CR in 40%, unconfirmed CR in 18%, and partial responses in 30% of patients. The estimated PFS is 89% at one year but falls to 64% at two years, suggesting a high rate of relapse over time. The estimated OS is 91% and 76% and one and two years, respectively.[7]

Treatment with R-HyperCVAD was associated with grade 4 hematologic toxicity in the majority (87%) of patients, including neutropenia (74%) and thrombocytopenia (68%). In addition, there was one probable treatment-related death due to colitis in SWOG-0213.[7] This mirrors the experience at MDACC, where patients faced serious hematologic toxicity, as well as a continuous pattern of relapse over time.[6]

MCL2: R-MaxiCHOP and R-HiDAC

At ASH 2007, Geisler and colleagues presented the final results from the 2nd Nordic MCL trial, which examined intensive immunochemotherapy with autologous stem-cell (ASC) support in patients with previously untreated MCL.[8] Findings of long-term EFS in the MCL-2 trial suggest, for the first time, that intensive immunochemotherapy with rituximab and high-dose AraC, coupled with *in-vivo* purged stem-cell support, may constitute a potentially curative therapy for MCL.[8]

In the phase II MCL-2 trial, 159 patients were treated with six cycles of rituximab plus alternating cycles of dose-intensified CHOP

(R-MaxiCHOP) and high-dose cytarabine (R-HiDAC). Patients who responded to induction immunochemotherapy also received BEAM/BEAC with in-vivo purged ASC support.

The MCL-2 trial builds on results of the MCL-1 trial, in which patients received induction therapy with four cycles of maxi-CHOP before BEAM/BEAC and ASCT. MCL-2 was designed to evaluate whether the addition of rituximab to induction therapy and the addition of high-dose cytarabine to *in vivo* purging would improve long-term outcomes in patients with newly diagnosed MCL.

In MCL-2, nearly all patients (96%) showed some response to induction therapy, including CR in 55% and PR in 41% of patients. In the intent-to-treat analysis, the five-year EFS and OS were 63% and 74%, respectively. Among patients who responded to induction therapy and completed treatment (n = 144), the five-year response duration was 72%. After five years, plateaus in EFS and OS emerged, suggesting continued favorable long-term outcomes.

Molecular analysis—performed in roughly half of patients (n = 77) who had primers available—confirms the clinical findings of MCL-2. Among these patients, 90% became PCR-negative within two months of transplant. Compared with patients whose PCR negativity did not persist for at least one year following transplant, those who remained PCR-negative for more than one year had a longer duration of clinical response ($P < .0001$).

Reflecting the differences in clinical findings, molecular findings were also different in the MCL-1 and MCL-2 trials. In the MCL-1 trial, only 12% of 42 stem-cell products were PCR negative following transplant. By comparison, 88% of stem cell products were PCR negative in the MCL-2 trial ($P < .001$).[8]

Conclusions:

At the 2007 ASH annual meeting, several new regimens for the first-line treatment of MM or MCL debuted with impressive results which will impact clinical practice. In the setting of MM, transplant-eligible patients now have a range of evidence-based choices for first-line therapy, including VTD, Rd, and VDR. For MM patients who are not eligible for transplant, VMP is a constitutes a promising new treatment strategy.

Among the investigational regimens for newly diagnosed MCL, the combination of rituximab and bendamustine provides an attractive combination of efficacy and safety. R-HyperCVAD has demonstrated high remission rates, but with the current regimen, responses are not durable, and hematologic toxicity remains severe. For patients with MCL in first remission, intensive immunochemotherapy with *in vivo* purged stem cell support offers unprecedented response rates and survival. Continued refinement of these regimens may allow patients to achieve more durable responses without excessive toxicity or erosion in quality of life.

II. Quality of Life: Developing a Risk-Benefit Ratio for Available Treatment Options for Multiple Myeloma

David H. Vesole, MD, PhD

Maintaining the optimal balance between treatment efficacy and treatment toxicity is a fundamental challenge in the care of patients with malignancies. Accordingly, treatment selection requires a thorough assessment of the risk-benefit ratios of available treatment options. Until recently, little data has been available on the quality of life implications of various MM therapies. In the absence of quality of life information, data on toxicity serves as a reasonable proxy to evaluate the potential effects of therapy on patients' physical and psychosocial functioning.

VISTA: Melphalan and prednisone (MP) versus MP plus bortezomib (MPV)

The recently presented VISTA trial demonstrated rapid and durable responses when bortezomib was added to MP. Compared with MP alone, MPV was associated with a much shorter time to response (4.2 months versus 1.4 months; $P < .001$), and a much longer response duration (12.8 months versus 24.0 months).[4]

In the MPV and MP arms, the ORR was 82% and 50%, respectively ($P < .000001$). MPV therapy was also associated with a high CR rate – 30% according to EBMT criteria, compared with 4% in the MP arm ($P < .000001$)—suggesting that MPV is a very potent regimen.

The marked survival advantage of MPV, observed in the initial analysis at 16 months, persisted through the second analysis at two years (Figure 1). In the MPV and MP groups, two-year OS was 83% and 70%, respectively. The superior survival following treatment with MPV versus MP was consistent across age groups, including patients younger than 75 years (84% versus 74%) and those aged 75 years and older (79% versus 60%).

Toxicities in the VISTA trial were not insignificant. Overall, 46% of patients in the MPV arm and 36% of patients in the MP experienced serious adverse events over the course of the trial. As expected, peripheral neuropathy was the major difference in toxicity. In the MPV arm, 13% of patients experienced grade 3 sensory neuropathy, and <1% reported grade 4 symptoms. By comparison, without bortezomib, peripheral neuropathy was nonexistent in the MP arm. Among those in the MPV arm who experienced peripheral neuropathy, 75% had improved or resolved symptoms by a median of 64 days. A similar resolution of symptoms was reported in the prior APEX trial with bortezomib alone.[9]

Additional grade ≥3 toxicities in the MPV and MP arms, respectively, included fatigue (8% versus 2%) and gastrointestinal complaints (20% versus <6%). Common grade 3 and 4 hematologic toxicities in the MPV and MP arms were neutropenia (40% versus 38%), thrombocytopenia (37% versus 28%), and anemia (19% versus 28%). Despite these differences, fewer patients treated with MPV versus MP required transfusions (26% versus 35%) or erythropoietin support (34% versus 42%).[4]

Several conclusions can be drawn from the VISTA trial, which was the largest phase III MP-based trial to date: MPV significantly prolonged survival and demonstrated superiority across all pre-specified efficacy endpoints and prognostic subgroups. The 54-week MPV treatment regimen was well-tolerated, with similar numbers of patients in the MPV and MP groups discontinuing therapy due to adverse events (14% in each arm).

Bortezomib and dexamethasone

Bortezomib has also been evaluated in combination with dexamethasone for first-line treatment in MM.[9] In a phase II study of this regimen, 32 consecutive symptomatic patients received treatment with bortezomib 1.3 mg/m^2 on days 1, 4, 8, and 11 of each three-week cycle for a maximum of six cycles. Those exhibiting suboptimal response to bort-

ezomib—defined as <PR after two cycles or <CR after four cycles—received additional treatment with oral dexamethasone 40 mg on the day of and the day following bortezomib administration.[10]

The ORR was 88%, including CR in 6% of patients and nCR in 19%. The median time to response was 2 months, or approximately 3 cycles. After a median follow-up of 5.5 months, the estimated one-year survival was 87%. Twenty-one patients completed all six cycles of bortezomib, and 26 patients completed at least five cycles. Dexamethasone was added in 22 patients, leading to 15 improved responses. Thus, alone or in combination with dexamethasone, bortezomib appears to be an effective induction therapy.

Treatment-related toxicities were manageable, with 40% of patients requiring a dose reduction at some point during the trial (median reduction, 25%). The most common ≥ grade 2 adverse events included sensory neuropathy (31%), constipation (28%), myalgia (28%), and fatigue (25%). In five of ten patients, grade 2/3 sensory neuropathy was reversible within a median of three months. Among the several patients who went on to transplantation following this trial, treatment with bortezomib did not adversely affect stem cell mobilization in eight patients, nor did not affect ASCT in six patients.

CALGB 10301: Bortezomib and pegylated liposomal doxorubicin

The combination of bortezomib and pegylated liposomal doxorubicin (PLD), an FDA-approved, steroid-free regimen for relapsed MM, has also been evaluated as first-line therapy. In the CALGB 10301 trial, 63 patients with newly diagnosed MM were received treatment with bortezomib 1.3 mg/m^2 on days 1, 4, 8, and 11, as well as PLD 30 mg/m^2 on day 4, for a maximum of eight 21-day cycles.[11] Among patients who completed at least two cycles of therapy (n = 57), nine patients (16%) achieved a CR or nCR, and 33 (58%) achieved a PR or better. Final response rates were higher among 29 patients who had completed therapy: 8 (28%) achieved a CR or nCR, and 23 (79%) achieved a PR or better.

Hematologic adverse events, including neutropenia, thrombocytopenia, lymphopenia, and anemia, reached grade 3 in 25% of patients and grade 4 in 9%. Notable non-hematologic adverse events included fatigue (16%, grade 3), sensory neuropathy (13%, [11%, grade 3; 2%, grade 4]), hand-foot syndrome (9%, grade 3), and syncope (9%, grade 3). All other toxicities were observed in ≤5% of patients. Overall, 58% and 9% of patients had grade 3 and 4 non-hematologic adverse events, respectively.[11]

Given these preliminary findings, combination therapy with bortezomib and PLD has promising activity and appears to be well tolerated in patients with newly diagnosed MM. Without a steroid component, this regimen avoids some of the toxicity characteristic of steroid-based therapies.

Bortezomib retreatment

At the 2007 ASH annual meeting, Hrusoversusky and colleagues reported findings from a retrospective analysis of patients with MM who had previously responded to bortezomib, subsequently presented with relapsed disease, and received bortezomib for a second time.[12] This retrospective analysis in 65 patients from 15 centers provided a revealing snapshot of bortezomib treatment responses in relapsed MM. Bortezomib was delivered at a dose of 1.3/m^2 in the majority of patients during both initial therapy (94%) and retreatment (86%). Concomitant treatment with dexamethasone was common, although it was given more frequently with bortezomib retreatment (62%) than with initial therapy (39%). The median number cycles during re-treatment was 4 cycles. Only six patients (12.2%) received another form of anti-myeloma therapy between initial therapy and bortezomib retreatment.

By protocol, 100% of patients responded to initial bortezomib treatment. Approximately two-thirds of patients (63%) also responded to bortezomib retreatment, suggesting a high level of activity during the second exposure to bortezomib. Other measures of treatment activity were similarly retained between initial therapy and retreatment, including CR rate (12% versus 10%) and median time to response (3.2 months versus 3.0 months), duration of response (6.3 months versus 4.5 months), treatment-free interval (6.6 months versus 4.1 months), and TTP (10.9 months versus 6.7 months).

The safety of bortezomib retreatment mirrors that of initial therapy. During retreatment, there were 11 cases of peripheral neuropathy (one mild, five moderate, and five severe), and seven cases of thrombocytopenia (two mild, two moderate, one severe, and two life-threatening).[12] Peripheral neuropathy—largely reversible in this analysis—typically can be lessened by appropriate dose reductions.

Bortezomib in renal impairment

Two trials have evaluated the clinical outcome of bortezomib-based therapies in patients with renal failure.[13, 14] Ailawadhi et al reported a retrospective study of 66 patients who were treated with combination therapies containing bortezomib 1.3 mg/m^2.[12] Clinical responses to bortezomib-based therapy were similar to those observed in other patient cohorts with normal renal function Importantly, no interactions were found between renal function and treatment response, age, gender, disease stage, Ig subtype, or disease status.[13]

Mulkerin reported a prospective phase I dose-escalation trial of 59 patients with advanced cancers, including MM (n = 14) and non-Hodgkin's lymphoma (n = 2).[13] Treatment was delivered on days 1, 4, 8, and 11 of each 21-day cycle, and doses were increased based on toxicities observed in the first treatment cycle.[14]

No dose-limiting toxicities were observed during the first cycle of bortezomib, even among patients on dialysis (n = 9). Although renal and metabolic abnormalities were more common among dialysis patients, the overall toxicity profile was similar among patients with normal renal function, those with mild-to-severe renal impairment, and those on dialysis.[14]

Together, these findings suggest that bortezomib is an effective therapy for MM patients with renal dysfunction.[13, 14]

IFM 01-01: Melphalan/prednisone with versus without thalidomide in elderly patients

The Intergroupe Francophone du Myélome (IFM) 99-06 trial[15] showed that MPT was superior to MP and to two courses of melphalan 100 mg/m2 with peripheral blood stem cell support. Subsequently, combination therapy with MPT has emerged as standard therapy for newly diagnosed patients aged 65 to 75 years. However, the clinical utility of adding thalidomide to MP has not been explored in patients older than 75 years. The IFM 01-01 trial was designed to compare MP with and without thalidomide in this older patient cohort.[16] In this study, 258 patients aged ≥75 years (median, 78.5 years) were treated with melphalan 0.2mg/

kg/d and prednisone 2 mg/kg/d on days 1-4 every six weeks for a maximum of 12 cycles. Patients were also randomly assigned to additional treatment with thalidomide 100 mg/day (n = 113) or placebo (n = 116).

After a median follow-up of 24 months, the addition of thalidomide provided greater response rates, PFS, and OS compared with MP alone. Rates of CR, VGPR, and ≥PR were 7%, 22%, and 62% in the MPT arm and 1%, 7%, and 31% in the MP arm (P < .0001). Median PFS in these groups was 24.1 months and 19 months, respectively (P = .001). Median OS was 45.3 months and 27.7 months with and without thalidomide, respectively (P = .03).

More patients in the MPT arm (53%) than in the MP arm (15%) discontinued treatment due to toxicity (P < .001), suggesting increased toxicity with the addition of thalidomide. In particular, patients receiving thalidomide, compared with those receiving MP alone, had higher rates of grade 1-3 peripheral neuropathy (38% versus 24%; P = .02), grade 3-4 neutropenia (21% versus 9%; P = .01), and grade 2-4 depression (8% versus 2%; P = .04). However, rates of DVT (6% versus 4%) and somnolence (6% versus 3%) were not significantly different in the two groups.[16]

To date, several clinical trials have examined melphalan/prednisone in combination with novel therapies such as thalidomide, lenalidomide, and bortezomib.[15, 17] For each of these regimens, there is a trade-off between increased potency at the cost of increased toxicities. For example, lenalidomide is myelosuppresive whereas thalidomide and bortezomib-based regimens tend to have excess peripheral neuropathy. Therefore, treatment decisions must be tailored to the comorbidities and concerns of individual patients, physician preference, patient preference and the logistics of administering the chemotherapy.

Lenalidomide/dexamethasone-based therapies

As described above, the ECOG-E4A03 trial compared lenalidomide in combination with high (40 mg days 1-4, 9-12, 17-20)- or low-dose (40 mg weekly) dexamethasone in patients with newly diagnosed MM.[2] The primary endpoint was response rate at 4 months.

The first interim analysis showed a non-significant trend toward improved response rates with high-dose dexamethasone (82%) compared with the low-dose dexamethasone (70%). However, the lower-dose regimen was associated with superior one-year survival: the probabilities of survival were 88% and 96% at one year (P = .003), and 75% and 87% at two years (P = .009) for the high-dose and low-dose arms, respectively.

An analysis of the patterns of mortality in ECOG-E4A03 clarifies the activity of these regimens. Whereas early deaths (<4 months) were more common in the high-dose group (5%) than in the low-dose group (0.5%; P = .01), the excess mortality observed in the high-dose group was attributed to both disease progression and toxicity. In addition, when OS was evaluated according to patient age, the survival advantage in the low-dose arm was apparent only in patients ≥65 years of age (P = 0.018), but not in patients <65 years (P = 0.20).

Expectedly, the high-dose treatment was associated with significantly greater toxicity. Among the non-hematologic adverse events, patients in the high-dose group were more likely than those in the low-dose group to have DVT/PE (25% versus 9%; P < .001), infection/pneumonia (14% versus 7%), and non-neuropathic weakness (10% versus 4%; P = .008). In contrast, other toxicities were comparable between the two groups.[2] On the basis of these findings, Rajkumar and colleagues concluded that all patients should be considered for low-dose dexamethasone when treated with lenalidomide-based regimens.

Bortezomib, lenalidomide, and dexamethasone

The phase I/II open-label study of bortezomib/lenalidomide/dexamethasone, described above, demonstrated the efficacy of this combination in patients with newly diagnosed MM. A preliminary report on 42 patients showed a remarkable ORR at 98% that included 21% CR , 7% nCR, and 24% VGPR.[3] Toxicities were significant in this patient population, reaching grade 4 for DVT (n = 1), thrombocytopenia (n = 2), and neutropenia (n = 2).

Grade 3 toxicities included metabolic abnormalities (n = 6), pneumonia (n = 3), infection (n = 3), liver function abnormalities (n = 3), dizziness (n = 2), cardiac symptoms (n = 2), and anemia (n = 2). The remaining grade 3 adverse events, occurring in one patient each, were chest pain, neuropathic pain, mental status abnormality, renal function abnormality, insomnia, lymphopenia, and leukopenia.[3]

A universal observation in patients treated with immunomodulatory agents, either thalidomide or lenalidomide, is the increased risk of DVT. The risk is highest in patients treated with high dose of steroids. Patients should be taking some form of anticoagulant, such as aspirin for standard risk patients and full anticoagulation (either warfarin or low molecular weight heparin) for high risk patients.[18]

Transplantation

To date, the comparison of novel agents to transplantation has not been studied. Thus, the optimal timing of transplantation needs to be re-assessed in the age of novel agents with their associated high response rates.

One issue raised was the optimal timing of the transplant. Two randomized studies comparing early versus late transplant at relapse showed comparable overall survival. Fernand et al in 1998, continues to inform treatment decisions one decade after it was first reported.[19] The multicenter randomized trial compared up-front or rescue treatment with high-dose therapy (HDT) and autologous peripheral blood stem cell transplantation in patients up to 56 years old.

Patients randomly assigned to the early HDT group (n = 91) received up-front treatment with three or four monthly cycles of VAMP, followed by HDT and PBSC autotransplantation regardless of disease response. Those assigned to the late HDT group (n = 94) received up-front conventional-dose chemotherapy (six cycles of VMCP). HDT and transplantation were reserved as rescue treatment in patients with primary resistance to VMCP, or delivered at relapse in responders. In all patients, peripheral blood stem cells were collected before randomization and after mobilization by chemotherapy.

After a median follow-up of 58 months, OS was equivalent in the early- and late-HDT groups (64.6 months versus 64.0 months; P = .92). In contrast, median EFS findings appeared to favor the early-HDT group. Median EFS in the early-HDT group was 39 months. In the late-HDT group, the interval between randomization and VMCP failure or death (Post-VMCP EFS) was 13 months. Quality of life, measured as the average time without symptoms, treatment, or treatment-related toxicity (TWiSTT), also favored the early-HDT group (27.8 months) compared with the late-HDT group (22.3 months).[19]

A second study by the United States Intergroup S9321 similarly showed compa-

rable EFS and OS between the early and late transplant groups.[20] More recently, the Dutch-Belgian Hemato-Oncology Cooperative Study Group (HOVON)-24 trial provided a different portrait of quality of life in patients undergoing autologous transplantation.[21] The randomized, multicenter, phase III trial compared the efficacy of intensified treatment with and without subsequent myeloablative therapy in 441 newly diagnosed patients.[21]

After induction with three to four cycles of vincristine, adriamycin, dexamethasone (VAD), patients were randomly issued to treatment with intermediate-dose melphalan (140 mg/m^2) without stem cell rescue (single-intensive therapy), or the same regimen followed by myeloablative treatment with cyclophosphamide (120 mg/kg) and TBI with autologous transplant (double-intensive therapy).

Although CR was higher among patients who received intensive chemotherapy and myeloablative therapy with autologous transplant compared with those who received intensive chemotherapy alone (28% versus 13%, P = .002), In addition, double intensive treatment resulted in a better event-free survival and progression-free survival but not overall survival compared to single non-myeloablative treatment in previously untreated patients with multiple myeloma.[22]

However, findings from this trial suggest that the benefits associated with myeloablative therapy are costly in terms of quality of life. [23] During the first year of follow-up, patients had a significant deterioration in both function and quality of life—as assessed quality of life questionnaire—after myeloablative therapy. Compared with patients who received intensified chemotherapy alone, patients who also received myeloablative therapy had worse overall quality of life (P < .05), role functioning (P < .05), and social functioning (P < .05), had more financial problems (P < .05), and were more likely to report pain (P < .05), loss of appetitive (P < .05), and fatigue (P < .001).[23]

After the first year of follow-up in the HOVON-24 trial, the balance in quality of life began to shift toward the double-intensive group. The improvement in quality of life observed after one year in patients who underwent transplantation is largely a function of longer remission durations in this treatment group.

Beyond data from these trials, little information is available regarding the quality-of-life implications in conventional therapy or transplantation in MM patients. Currently, quality of life assessments are now routinely incorporated into most clinical trial designs. As ongoing trials begin to report quality of life data, clinicians will have additional evidence to inform their treatment decisions in this patient group.

Conclusions

Treatment options for patients with newly diagnosed MM have steadily improved over the last several years, with average one-year survival rates now exceeding 90% with virtually all of the current regimens (Table 2). Most recently, findings from ECOG-E4A03 demonstrate a one-year survival of 96% following treatment with lenalinomide and low-dose dexamethasone.[2] This is a dramatic improvement from just two years ago, when the most promising novel therapy—thalidomide and dexamethasone—provided an average one-year survival of 80%.[24]

These tremendous gains in survival are a major accomplishment for the MM community. New research strategies will likely focus on reducing the toxicities associated with live-saving treatment. In the meantime, the choice of treatment may depend on the toxicity profiles of different regimens. For example, different options may be more appropriate for patients with certain comorbid diseases or conditions, such as preexisting neuropathy or renal insufficiency. In addition, decisions may be driven by differences in treatment schedules and administration. Some patients may have a preference for regimens that require fewer office visits, whereas some physicians may prefer intravenous administration for patients whose compliance to oral therapy may become a barrier to optimal treatment. As MM becomes a chronic disease, preserving long-term quality of life is an important treatment goal.

Table 2. One-year survival rate in phase III trials of newly diagnosed multiple myeloma

Study	Age	Phase	N	Regimen	1-yr Survival rate	Ref
Rajkumar, E1A00	Median = 65	III	103	Thal Dex vs Dex	80%	JCO 2006
Rajkumar, MM003	Median = 65	III	470	Thal Dex vs Dex	80%	ASH 06
Palumbo	Median = 72	III	255	MPT vs MP	87%~	Lancet 06
Facon, IFM 99-06	65-75	III	447	MPT vs MP vs Mel 100	88%~	ASCO 06
Attal, IFM	<65	III	200	Auto vs Chemo	88%~	NEJM 1996
Child, MRC	<65	III	401	Auto vs Chemo	87%*	NEJM 2003
Barlogie, S9321	≤70	III	516	Auto vs Chemo	84%*	JCO 06
Attal, IFM	<60	III	399	Single vs Double Auto	90%~	NEJM 2003
Barlogie, TT II	<75**	III	668	TT2 ± Thal	92%	NEJM 2006
E4A03 Arm A	Median = 65	III	223	Len + high-dose dex	87%	ASCO 2007
E4A03 Arm B	Median = 65	III	222	Len + low-dose dex	96%	ASCO 2007

*Intent to treat population.

**80% age <65.

Auto indicates autologous stem cell transplant; Chemo, chemotherapy; Dex, dexamethasone; Len, lenalidomide; MP, melphalan/prednisone; MPT, melphalan/prednisone + thalidomide; Thal, thalidomide; TT2, total therapy 2.

Adapted from Rajkumar SV, Jacobus S, Callander N, et al. Phase III trial of lenalidomide plus high-dose dexamethasone versus lanolidomide plus low-dose dexamethasone in newly diagnosed multiple myeloma (E4A03): a trial coordinated by the Eastern Cooperative Oncology Group. Abstract presented at: Annual Meeting of the American Society of Clinical Oncology. 2007; Chicago, IL. Abstract LBA8025.

III. Current and Future Treatment Options for MCL and the Role of Transplantation

Christopher Flowers, MD, MSc

MCL is a discrete subtype comprising 6%–8% of newly diagnosed NHL. According to data from the Surveillance, Epidemiology, and End Results (SEER) registry, 5.29 new cases of MM per 100,000 persons are reported each year, whereas the annual rate of incident cases of MCL is only 0.51 per 100,000 persons.[25] However, given that MCL is a form of NHL that is difficult to manage, with a median survival of 3 to 4 years, treatment strategies for MCL are the focus of intense research efforts.

Approaches to First-line therapy

Although MCL is responsive to standard CHOP chemotherapy, the durations of response tend to be limited, leading to the characteristic relapsing and remitting course of disease. Similar to approaches used for other B-cell lymphomas, attempts to improve on first-line therapy with CHOP have involved addition of the monoclonal antibody rituximab (R).[26] In a prospective study of 122 subjects with newly diagnosed MCL run by the German Lymphoma Study Group, patients were randomly assigned to treatment with CHOP (n = 60) or R-CHOP (n = 62).[26]

The addition of rituximab to CHOP, compared with CHOP alone, increased the ORR (94% versus 75%; *P*=0.005), increased the CR rate (34% versus 7%; *P* = .00024), and extended the TTF (21 months 14 months with CHOP; *P* = .0131). R-CHOP also was a well-tolerated regimen for frontline therapy of MCL with similar rates of infections (7% versus 5% with CHOP). However, these benefits did not translate to improvements in OS.[26]

Provocative data from the first interim analysis of the phase III StiL trial comparing bendamustine 90 mg/m^2 day 1 and 2 and rituximab 375 mg/m^2 day given every four weeks (BR) and R-CHOP in patients with MCL and indolent NHLs, suggested that BR may have similar efficacy, and slightly less toxicity. In 33 patients receiving BR the ORR was 88% and CR rate was 42% compared with R-CHOP (n = 27; ORR 96%, CR 41%). [5] Still, both regimens provide only modest complete responses in limited numbers of MCL patients.

In an Eastern Cooperative Oncology Group trial, R-CHOP has also been combined with ^{90}Y-ibritumomab tiuxetan for upfront treatment of MCL, to improve upon these outcomes. In 50 subjects completing therapy, 52% experience CR/CRu. [27] These trials provide potential regimens that may be modified in developing more effective and less toxic future frontline regimens.

R-HyperCVAD

In a phase II trial of 45 patients with untreated or relapsed MCL, Khouri and colleagues from the MD Anderson demonstrated that intensified chemotherapy with hyperfractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone (HyperCVAD) alternating with regimens using high-dose methotrexate and cytarabine, and followed by stem-cell transplantation was at least as effective as historical controls who received CHOP for primary therapy (n = 25).[24] Among those who had no prior treatment for MCL (n = 25), this approach increased three-year EFS (72% versus 28% with CHOP; *P* = .0001) and three-year OS (92% versus 56% with CHOP; *P* = .05).[28]

Building on these promising findings, researchers at the MDACC added rituximab to hyperCVAD (R-HyperCVAD).[6] In a prospective phase II trial, 92 patients with stage IV MCL received treatment with alternating three-week cycles of the following two regimens:

- R-HyperCVAD (given week 1 and then every 6 weeks for 4 cycles)
  - Rituximab 375 mg/m^2 day 1
  - Cyclophosphamide 300 mg/m^2 days 2-4
  - Doxorubicin 16.6 mg/m^2 days 5-7
  - Vincristine 1.4 mg/m^2 days 5, 12
  - Dexamethasone 40 mg days 2-5 and 12-15
- Rituximab plus high-dose methotrexate-cytarabine (given on week 4 and then every 6 weeks for 4 cycles)
  - Rituximab 375 mg/m^2 day 1
  - Methotrexate 200 mg/m^2 day 2 IV per bolus
  - Methotrexate 800 mg/m^2 day 2 IV continuous infusion
  - Cytarabine 3000 mg/m^2 day 3-4 (reduced by 2/3 when creatinine >1.5 mg/dL and in all patients aged >60 years)

Patients (mean age, 61 years) also received comprehensive prophylaxis with mesna, calcium, leucovorin, prednisone eyedrops, granulocyte colony-stimulating factor (G-CSF), and antibacterial, antifungal, and antiviral therapy. After the first six cycles, the ORR was 97%, including CR or unconfirmed CR (CRu) in 87% of patients, and PR in 10% of patients. With a median follow-up of 40 months, the three-year failure-free survival (FFS) and OS were 64% and 82%, respectively.

Patients aged ≤65 years had better outcomes than those aged >65 years. The median FFS rate in these age groups were 73% and 50%, respectively, after 40 months (*P* = .02). In addition to age >65 years, elevated β2 microglobulin levels, elevated lactate dehydrogenase (LDH), and >2 IPI risk factors predicted worse FFS. However, hematologic toxicity associated with this intensive therapy was significant. During treatment, five patients died from acute toxicities, including sepsis (n = 3), pulmonary hemorrhage (n = 1), and unknown cause (n = 1). Four patients developed myelodysplasia/acute myelogenous leukemia after treatment and while in CR. Three of these patients died, for a total of 8 deaths (8%) at the time of the analysis.

Despite the automatic per-protocol reduction in cytarabine dose in older patients, significantly more patients >65 years of age than ≤65 required further dose reductions due to adverse events (*P* = .00001). Given the increased toxicity and shorter FFS observed in the older cohort, alternating cycles of R-hyper-CVAD and rituximab plus high-dose methotrexate and cytarabine should not be considered standard therapy for patients >65 years old.[6]

Recently the Southwest Oncology Group performed a confirmatory, multi-institutional phase II study of 49 patients with newly diagnosed MCL.[7] SWOG-0213 evaluated the MDACC protocol—R-HyperCVAD alternating every 21 days with rituximab plus high-dose methotrexate-cytarabine—for a total of eight cycles in patients with nodular (6%), diffuse (27%), mantle zone (57%), or blastic (8%) variants of MCL.[7] The preliminary results of this trial presented at the American Society of Hematology annual meeting in 2007 showed an ORR of 88%, including CR in 40%, unconfirmed CR in 18%, and PR in 30% of patients (Table 3). One-year PFS was 89% falling to 64% at two years. Again, investigators found

Table 3. SWOG-0213: R-HyperCVAD in newly diagnosed MCL

	Number of patients (%)	
Response		
ORR	35 (88%)	
CR	16 (40%)	
CRu	7 (18%)	
PR	2 (30%)	
Stable/no response	2 (5%)	
Survival		
1-year PFS	89%	
2-year PFS	63%	
1-year OS	91%	
	Grade 3	Grade 4
Hematologic toxicity		
Anemia	28 (60%)	6 (13%)
Thrombocytopenia	9 (19%)	32 (68%)
Neutropenia/ granulocytopenia	5 (11%)	35 (74%)
Leukopenia	1 (2%)	39 (83%)
Non-hematologic toxicity		
Infection (with grade 3/4 neutropenia)	15 (32%)	1 (2%)
Hyperglycemia	2 (15%)	1 (2%)

CR indicated complete response; CRu, complete response unconfirmed; MCL, mantle cell lymphoma; ORR, overall response rate; OS, overall survival; PR, partial response; PFS, progression-free survival; R-HyperCVAD, rituximab + fractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone.

Adapted from Epner EM, Unger J, Miller T, et al. A multi center trial of hyperCVAD + rituxan in patients with newly diagnosed mantle cell lymphoma. Abstract presented at 49th Annual Meeting of the American Society of Hematology. 2007; Atlanta, GA. Abstract 387.

marked hematologic toxicity with this intensive regimen. The majority of patients experienced grade 4 leukopenia (83%), neutropenia/granulocytopenia (74%), and thrombocytopenia (68%). Among patients with grade 3-4 neutropenia, 32% had grade 3 infections and 2% had grade 4 infections. The low rate of grade 4 infection may be attributed to the prophylactic regimen that is given as part of the protocol.[7]

Modified R-HyperCVAD with rituximab maintenance therapy

Although R-HyperCVAD yields high overall and complete response rates, this intensive regimen is prohibitively toxic for some patients with MCL.[6] Given these previous findings, Kahl and colleagues from the Wisconsin Oncology Network (WON) hypothesized that preserving rituximab but removing methotrexate and cytarabine from the induction HyperCVAD regimen might produce high response rates with acceptable toxicity. Furthermore, maintenance therapy with rituximab was added as an attempt to extend PFS beyond that observed in earlier trials.

To test this hypothesis, the WON initiated a phase II study of modified R-HyperCVAD (without methotrexate or cytarabine) administered every 28 days for four to six cycles.[29] Patients achieving at least a PR following induction therapy received maintenance therapy with four weekly doses of rituximab every 6 months for 2 years.

Twenty-two patients (mean age, 63 years) with histologically confirmed CD20+ MCL and a PS of 0 to 2 enrolled in the trial. Prior to study entry, patients could not have received more than 1 cycle of CHOP-like therapy for MCL. Responses and long-term clinical outcomes were promising. The ORR was 77%, including CR/CRu in 64% of patients. With a median follow-up of 37 months the OS has not been reached; the median PFS was 37 months. Among 15 patients with sufficient data to assess molecular responses, nine achieved molecular remissions and five maintained molecular CR throughout maintenance.

During induction therapy, the major adverse event was myelosuppression. Grade 4 events reported across 104 cycles of induction therapy included neutropenia (n = 41), thrombocytopenia (n = 2), and anemia (n = 1). One patient died following infection during neutropenia, and one patient died following colonic perforation. No major toxicities were reported during maintenance therapy with rituximab, suggesting that this may be a reasonable strategy for older patients. Overall, the WON concluded that this approach is worthy of additional study in MCL.[29]

Intensive therapy with transplantation following chemo-immunotherapy

Another recent line of investigation has focused on the combination of intensive chemotherapy, rituximab, and stem cell transplantation. Researchers at the University of Nebraska Medical Center (UNMC) undertook a retrospective analysis to compare outcomes of patients who received one of two treatment regimens: induction therapy with HyperCVAD and high-dose methotrexate and cytarabine, with or without rituximab, followed by ASCT; or CHOP-like therapy, with or without rituximab, followed by ASCT (Figure 2).[30]

In the retrospective case series, 80 patients with MCL received high-dose chemotherapy and an autologous stem cell transplant in first complete remission (n = 47) or partial remission (n = 33). The patients received either CHOP-like induction therapy, with or without rituximab (n = 48), or HyperCVAD and high-dose methotrexate/cytarabine, with or without rituximab (n = 32).[30]

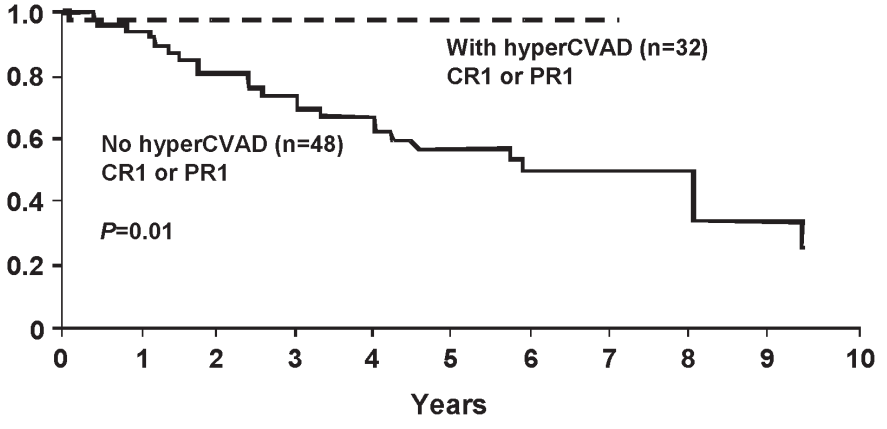

Figure 2. Overall survival following ASCT according to HyperCVAD induction response. ASCT indicates autologous stem cell transplant; CR1, first complete remission; HyperCVAD, fractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone; PR1, first partial remission. Reprinted from Vose J, Loberiza F, Bierman P, et al. Mantle cell lymphoma (MCL): Induction therapy with HyperCVAD/High-dose methotrexate and cytarabine (M-C) (±rituximab) improves results of autologous stem cell transplant in first remission. Abstract presented at: Annual Meeting of the American Society of Clinical Oncology. 2007; Chicago, IL. Abstract 7511.

Results were significantly in favor of induction therapy with HyperCVAD and high-dose methotrexate/cytarabine. Compared with patients in the CHOP-like induction group, patients in the HyperCVAD induction group had higher PFS at one year (76% versus 97%) and two years (55% versus 78%), and higher OS at two years (68% versus 97%). By multivariate analysis, improved OS was associated with the following characteristics: receiving HyperCVAD induction (P = .04), transplant in first remission (P = .009), < 3 prior chemotherapy regimens (P = .02), and no B symptoms at transplant (P = .05).[30]

Patients included in this analysis were treated in the community setting, typically for a limited duration of four cycles.[30] As a retrospective analysis of data gathered from referrals to UNMC for transplantation , this study does not share in the statistical rigor of randomized, prospective trials and can be subject to referral biases. However, these data do provide a real-world picture of the outcomes when CHOP-based chemotherapy or HyperCVAD are delivered in community setting prior to referral to a transplant center. Overall, findings from the UNMC retrospective analysis support the use of Hyper-CVAD and high-dose methotrexate/cytarabine, with or without rituximab, as induction therapy for eligible patients prior to planned ASCT in first remission.

Although there remains some controversy regarding the ideal strategy for the initial treatment of MCL[31], other trials also support the benefits of upfront autologous stem cell transplantation for patients with MCL following aggressive induction chemotherapy with regimens containing rituximab and high-dose cytarabine.[32,33]

Second-line therapy

^{90}Y-ibritumomab tiuxetan

In 2005, Younes et al reported findings from a trial of 90Y-ibritumomab tiuxetan in 26 patients with relapsed or refractory MCL.[34] Upon entry, all patients (median age, 70 years) had an ECOG PS of 0 or 1, and 22% had bulky disease (≥5 cm). The stage distribution was: II (33%), III (27%), and IV (40%). Patients had a median of 3 prior regimens (range, 1 to 6), although prior treatment with radioimmunotherapy or high-dose therapy and ASCT was not permitted. Dosing of 90Y-ibritumomab tiuxetan was based on baseline platelet count: 0.3 mCi/kg for platelet counts of 100,000-149,000/mm^3, and 0.4 mCi/kg for platelet counts ≥150,000/mm^3.

The ORR was 35%, including CR/CRu in 22% of patients and PR in 13% of patients. The median PFS was 9 months, and the median DR was 9.5 months. Patients with bulky disease did not respond to therapy. The primary toxicity associated with ^{90}Y-ibritumomab tiuxetan treatment was myelosuppression, including neutropenia in 48% of patients. The median platelet and neutrophil nadirs occurred 41 and 48 days after therapy, respectively. Seven patients (30%) required platelet transfusions, and one patient was hospitalized for febrile neutropenia and sepsis. [34]

Bortezomib

The FDA approval of bortezomib for previously treated MCL was based largely on findings from the phase II PINNACLE trial.[35] In 2006, Fisher and colleagues presented initial findings from the trial, in which 155 patients with relapse or refractory MCL were treated with bortezomib 1.3 mg/m^2 on days 1, 4, 8, and 11 of each 21-day cycle, for up to 17 cycles. Among 141 evaluable patients, the ORR was 33%, including a CR/CRu in 8% of patients. Median TTP and DOR were 6.2 months and 9.2 months, respectively. After a median follow-up of 13.4 months, median OS had not been reached.[35]

At the 2007 ASH annual meeting, Goy et al presented additional survival data from the PINNACLE trial after a median follow-up of 26.4 months.[36] One-year survival was 69% in the entire study cohort, and 91% among responding patients. Median OS was 23.5 months among all patients, and 35.4 months among responders. The most common grade 3/4 adverse event was peripheral neuropathy (13%), which occurred at a median time to onset of four treatment cycles. Four treatment-related deaths were observed, including death from non-neutropenic sepsis (n = 3) and respiratory failure (n = 1).[36]

Given in a variety of doses, bortezomib produces a clinically meaningful duration of response as second-line therapy in MCL.[27,28] Given its activity in the relapsed setting, bortezomib is also being evaluated as first-line therapy alone and in combination with R-CHOP chemotherapy[37] and modified R-HyperCVAD. Such regimens may offer a therapy with high response rates and a less toxic alternative to some of the more intensive regimens involving high dose cytarabine that have been examined in MCL.

Conclusions

First-line autologous stem cell transplant may provide benefits for younger patients with MCL. Adding rituximab and high-dose methotrexate and cytarabine to induction therapy prior to ASCT appears to improve outcomes further. Finally, novel agents such as bortezomib have shown benefits in the relapse setting. Such agents may emerge as lower-toxicity alternatives to therapies currently used in first-line regimens and may be added to existing front-line regimens to improve outcomes.

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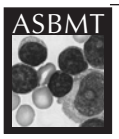

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