

Ten Years of Improvement in the Management of Multiple Myeloma: 2000-2010

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Abstract

In 2000, the most important therapeutic improvement in multiple myeloma (MM) had been the introduction of high-dose therapy (HDT) supported by autologous stem cell transplantation, but this strategy was proposed only to younger patients without comorbidities. In the past decade, progress in the management of MM has been dramatic and more rapid than in the four previous decades. The main reason for this has been the introduction of three novel agents in less than five years. These three agents, two immunomodulatory agents (IMiDs; thalidomide and lenalidomide) and one proteasome inhibitor (bortezomib) have been initially used in relapsed or refractory patients and rapidly added to frontline therapy both in younger and older patients. They have already increased overall survival but are also changing the objectives of treatment and the therapeutic strategy; other important advances have been made during these ten years with new diagnostic and staging procedures and new prognostic factors. These clinical improvements have been possible mostly by a better understanding of the disease pathophysiology, including genetic changes, and by the development of preclinical in vitro and vivo tests to better evaluate the potential clinical activity of new agents.

Clinical Lymphoma, Myeloma & Leukemia, Vol. 10, No. 6, 424-442, 2010; DOI: 10.3816/CLML.2010.n.076

Keywords: Diagnostics, Disease staging, Genetic changes, Pathophysiology, Serum free light chain assay

New Diagnostic and Staging Procedures

Serum Free Light Chain Assay

The serum immunoglobulin free light chain (FLC) assay was developed in the early 2000s.¹ This highly sensitive quantification of free κ and λ chains is based on a commercial reagent set of polyclonal antibodies and is performed on automated nephelometric platforms. The assay consists of 2 separate quantifications of serum κ and λ FLC. An abnormal κ/λ ratio supports the presence of clonal plasma cell expansion.² Serum FLC assay has rapidly moved into clinical practice because of its sensitivity and its ease of performance. It is sometimes used too widely and it appeared useful in determining guidelines to avoid undue prescriptions.³

There are currently 3 major indications for the serum FLC assay in the management of multiple myeloma (MM) and related disorders.³

Diagnosis and Screening. Serum FLC assay should now be included in the screening for monoclonal proteins and can replace 24-hour urine studies for all diagnoses except light chain amyloidosis.^{3,4} Serum FLC can help in the diagnosis of oligosecretory myeloma⁵ and has

been included in the revised definition of MM by the International Myeloma Working Group (measurable disease is defined by an involved FLC ≥ 100 mg/L with an abnormal κ/λ ratio).⁶

Prognosis. The prognostic value of the serum FLC assay has been shown in monoclonal gammopathy of undetermined significance (MGUS),⁷ smoldering myeloma,⁸ solitary plasmacytoma,⁹ MM,¹⁰⁻¹³ and amyloidosis.¹⁴

Response Assessment and Monitoring. The test should be used to assess response to treatment in patients with nonsecretory or oligosecretory MM and with amyloidosis. The role of serum FLC in evaluating response in light chain MM is more controversial, because the correlation between serum FLC assay and 24-hour urine electrophoresis is not validated.³ In patients with intact measurable M-component, the major role of serum FLC for response assessment is in patients who have achieved complete response (CR) with negative immunofixation: in 2006, normalization of κ/λ ratio was incorporated by the International Myeloma Working Group into the uniform response criteria to define a stringent CR level.⁶ However there is no convincing evidence that stringent CR is associated with better outcome compared with CR, and results of immunofixation and of serum FLC may be discordant.¹⁵

Imaging Techniques

Recently the International Myeloma Working Group published guidelines regarding the current role of imaging techniques in

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Submitted: Sep 2, 2010; Revised: Nov 2, 2010; Accepted: Nov 4, 2010

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the diagnosis and monitoring of MM.¹⁶ This consensus statement confirmed that conventional radiography remains the gold standard for staging purposes. Magnetic resonance imaging (MRI) provides additional information and is recommended in patients with normal conventional skeletal survey and in patients with solitary plasmacytoma of bone. Urgent MRI or computed tomography is the procedure of choice to assess suspected spinal cord compression. Two new techniques have emerged in the past 10 years: ¹⁸F-fluorodeoxyglucose positron emission tomography computed tomography (FDG PET/CT) and whole-body MRI. Both FDG PET/CT and whole-body MRI are more sensitive than conventional skeletal x-ray in diagnosing and screening MM.^{17,18} They provide information in areas that are not covered by MRI.¹⁹ Persistence of focal FDG PET/CT lesions after initial therapy may be associated with inferior outcome.²⁰ However, in the absence of large prospective clinical trials evaluating their prognostic effect, these new techniques are not yet recommended for routine use.

New Prognostic Factors

Although MM remains a fatal disease, with exceptional cases of possible cure, it is characterized by an extraordinary heterogeneity in outcome, with life expectancy from a few weeks up to 10 years. Several prognostic factors have been described, some associated with the tumor mass, others associated with the intrinsic biology of the malignant plasma cell. More recent prognostic models have included genetics, similarly to other hematologic malignancies.

International Staging System

Many prognostic classifications have been developed and over many years. The most widely used staging system has been the Durie-Salmon classification, which was based on the tumor mass evaluation (M-component quantification, presence of anemia, and number of bone lesions on standard x-rays) and on renal function. Among other parameters, β_2 -microglobulin (β_2 M) level was also considered a very strong prognostic factor.

In 2005, on behalf of the International Myeloma Foundation, a simple prognostic model has been reported, known as the "International Staging System (ISS)."²¹ To build this model, authors gathered biologic data from > 10,000 patients treated in 17 institutions or groups. They determined a 2-variable prognostic model, based on the β_2 M and albumin levels. The model identifies three groups of patients, with an increasing risk of early death. Stage I is defined by a β_2 M level < 3.5 mg/L and an albumin level > 35 g/L. Stage 3 is defined by a β_2 M > 5.5 mg/L. Stage 2 is defined by patients who do not meet criteria for stages 1 or 3. The median survival for patients with stages 1, 2, and 3 disease was 62, 44, and 29 months, respectively. The ISS is a major improvement over the Durie-Salmon system because it defines cohorts of patients with easily measurable, objective, and reproducible parameters. This model is now widely used in clinical trials. However, the ISS does not appear to improve the prediction of outcome compared with the Durie-Salmon classification and neither system accurately predicts the heterogeneity in patient survival.²² Therefore other prognostic factor classifications are still needed.

New Prognostic Factors

Cytogenetic Abnormalities. In the past 10 years cytogenetics have become one of the most important prognostic factor in MM, as is

the case in many other hematologic malignancies. This is mostly because of the wider use of fluorescence in situ hybridization (FISH). Conventional cytogenetics is indeed hampered by the low percentage of plasma cells present in the bone marrow sample and the low mitotic index of malignant plasma cells. Conventional chromosome banding can detect an abnormal karyotype in only 30%-40% of patients, and a normal karyotype mostly originates from normal hematopoietic cells. With conventional cytogenetics, hypodiploidy and chromosome 13 deletions are negative prognostic factors both with conventional-dose therapy and high-dose therapy (HDT).²³⁻²⁵

Fluorescence in situ hybridization can detect specific chromosome changes in purified plasma cell populations even in non-cycling interphase cells and detects abnormalities that are not detected by conventional karyotyping. By FISH, hyperdiploidy is associated with a better prognosis. Several FISH abnormalities have been associated with a poorer outcome, even with HDT. The most frequent are: del(13), present in 45%-50% of cases²⁶⁻²⁹; t(4;14), in 14%-18%³⁰⁻³⁶; and del(17p), in 11%-15%³⁵⁻³⁷. Others are less frequent and therefore less frequently evaluated by specific probes: abnormalities for chromosome 1p and 1q,³⁸⁻⁴⁰ and t(14;16).^{34,38-40} Although del(13) is a poor prognostic factor in all published series, its specific prognostic effect is unclear when detected only by FISH. It appears to be associated with a poor outcome only when associated with t(4;14) or del(17p).³⁷

Another frequent translocation t(11;14) does not appear to significantly affect the outcome.³⁵⁻³⁷

These parameters are now widely used for risk assessment and in clinical trials for the stratification in patient randomization and for clinical results comparison. Combinations of β_2 M level and presence of genetic abnormalities are powerful classifications for prognosis.^{29,37} For instance, the survival of patients with t(4;14) and/or del(17p), especially if combined with a high β_2 M level, is in the 18-24-month range, even with tandem-intensive strategies.³⁷ The most relevant cytogenetic abnormalities have been recently classified for clinical purpose.⁴¹

Gene Expression Profiling and Copy Number Changes. With the development of high-throughput genetic tools, it becomes possible to interrogate several thousands of markers at the same time, enabling one to achieve a more powerful system for prognostication. The first models have used gene expression profiling to find genes whose deregulation is associated with a good or poor prognosis. Actually, because the follow-up of the cohorts is usually short, most models have been focused on predicting short survival.⁴² Two models have been published, one based on 17 genes⁴³ and the second on 15 genes.⁴⁴ Although no common gene is present in each model, they are both equally effective on control patient cohorts. More recently, data have been reported using deoxyribonucleic acid microarrays to analyze the gains and losses of genetic material throughout the whole genome.⁴⁵ These techniques, known as comparative genomic hybridization array or single-nucleotide polymorphism array, are currently used to identify a small set of copy number changes that could be analyzed by FISH.⁴⁶ While there is no doubt that these new genetic tools will be used more frequently in the future, they are currently too expensive to be proposed in clinical practice. Furthermore, we have to keep in mind that most

Table 1 Pioneering Phase II Studies With Novel Agents Given as Simple Agents in Relapsed/Refractory Multiple Myeloma

Study Characteristic	Thalidomide	Bortezomib				Lenalidomide
	Singhal et al ⁵¹	Richardson et al ⁵²	Jagannath et al ⁵³		Richardson et al ⁵⁴	
	200-800 mg	1.3 g/m ²	1.0 g/m ²	1.3 g/m ²	15 mg Twice Daily	30 mg Daily
Schedule Administration	Daily	Days 1, 4, 8, 11	Days 1, 4, 8, 11		Days 1-21	Every 28 days
Number of Patients	84	193	28	26	35	67
Age	38% > 60 years	Mean, 60 years	Mean, 64 years	Mean, 60 years	Median, 59 years	Median, 60 years
Time Since Diagnosis	21% > 60 months	Median, 4 years	Median, 2 years	Median, 2 years	—	—
Number of Previous Therapies	NA	Median, 6	Median, 3	Median, 3	> 3, 60%	> 3, 53%
Previous ASCT	90%	64%	34%	42%	57%	63%
Previous Thalidomide	—	83%	32%	27%	80%	73%
Previous Bortezomib	—	—	—	—	21%	16%
Refractory to Last Therapy	—	91%	NA	NA	57%	48%
PR	24%	27%	30%	38%	14%	18%
MR	32%	35%	33%	50%	29%	24%
CR or nCR	2%	10%	11%	4%	0%	6%
Median TTP or PFS	3 months	6.6 months	7 months ^a	11 months ^a	3.5 months	8.3 months
Median Response Duration	> 14.5 months	12 months	9.5 months	13.7 months	20 months	20 months

^aBortezomib alone or with dexamethasone.

Abbreviations: ASCT = autologous stem cell transplantation; CR = complete response; MR = minimal response; nCR = near-complete response; PFS = progression-free survival; PR = partial response; TTP = time to progression

of these prognostic models have been built in the era of 'old conventional drugs.' Some data are suggesting that the novel drugs may overcome some of these prognostic parameters. This would mean that all of these models should be revisited for patients treated with the novel therapies.

Novel Agents in Relapsed Multiple Myeloma

The use of immunomodulatory agents (IMiDs; thalidomide, lenalidomide) and of bortezomib, the first-in-class proteasome inhibitor, has changed the landscape in the treatment of relapsed MM.⁴⁷ While the therapeutic activity of thalidomide has been shown almost empirically, the development of the other two agents has followed a more traditional approach with preclinical evaluation rapidly followed by phase I and phase II studies and by large randomized phase III trials. The ability of these drugs to overcome resistance to conventional agents has been shown in preclinical models⁴⁸⁻⁵⁰ and confirmed in clinical trials,⁵¹⁻⁵⁵ leading to FDA and EMEA approvals of all three agents in the treatment of relapsed MM. Results of pioneering phase II trials showing the clinical efficacy of the three drugs when used as single agents in relapsed/refractory patients are in Table 1.

Thalidomide

Comprehensive reviews on the use of thalidomide have been published and include efficacy and safety in relapsed MM.^{56,57} In 1999, the Arkansas group was the first to report on the efficacy of thalidomide as a single agent at a dose range of 200 to 800 mg per day, with an overall response rate of 25% in heavily pretreated patients.⁵¹ The rationale for using thalidomide was based on its

antiangiogenic properties because, in MM, increased microvessel density has been correlated to survival.⁵⁸ However, thalidomide has multiple modes of action, including immunomodulatory effects.^{50,59} This initial experience generated a great enthusiasm, and a large number of phase II trials were rapidly conducted. A systematic review of 42 such trials on > 1600 patients confirms that the response rate is 29% with an estimated 1-year overall survival (OS) of 60%.⁶⁰ The well-known teratogenicity of thalidomide is not a major concern in patients with MM because of patient age, but justifies careful information of patients and programs to avoid drug exposure in women of childbearing potential. The major toxicities of thalidomide are fatigue, somnolence, constipation, and mostly peripheral neuropathy, which is related to the daily dosage and to treatment duration.^{56,57} The overall incidence of peripheral neuropathy is 30% but may be higher if treatment is prolonged for > 1 year. Because this complication may be disabling and sometimes irreversible, patients should decrease the dose or stop treatment if significant paresthesia or numbness occurs.⁶¹

Thalidomide has been rapidly combined with dexamethasone or cytotoxic agents with the objective of increasing efficacy and of reducing toxicity by decreasing the daily dosage. The combination of lower doses of thalidomide (100-200 mg/day) with dexamethasone does apparently increase the response rate to 45%. Combination with cytotoxic agents (alkylating agents such as melphalan or cyclophosphamide, or anthracyclines) may be even more active (60%-65% response rate).^{56,57} However, until now no randomized study has been conducted to confirm the superiority of combinations versus single agents. Moreover, combinations have increased infections, and generated a new and unexpected adverse event, ie, deep vein thrombosis/pulmonary embolism. The

incidence of this complication is up to 15% with dexamethasone and up to 30% in anthracycline-containing regimens.^{56,57} The risk is higher in patients with a high tumor burden, and prophylaxis with low-molecular-weight heparin or oral anticoagulants should be considered in high-risk patients.^{57,62}

Bortezomib

Bortezomib is the first agent of a new class, proteasome inhibitors, that has demonstrated significant *in vitro* and *in vivo* activity on myeloma cell lines and in murine models.^{63,64} These studies led to the rapid development of this drug in relapsed MM. Two phase II studies (SUMMIT and CREST trials) have shown that, in heavily pretreated patients, response rate with bortezomib alone is 25%-30% and can be increased to 45%-50% with the addition of dexamethasone.^{52,53} Following these studies, the drug has been rapidly approved in the United States and Europe. It is administered intravenously at a dose of 1.3 mg/m² on days 1, 4, 8, and 11 of 28-day cycles. The large randomized phase III APEX trial has demonstrated that bortezomib is superior to dexamethasone in patients with relapsed disease, in terms of response rate, time to progression (TTP), and OS.⁶⁵ This superiority was confirmed in a subanalysis focusing on patients having received only 1 line of treatment (first relapse).⁶⁶ In an updated analysis of this trial, the response rate was 43% and the CR rate was 9%, with a benefit in median survival of 6 months (29.8 months vs. 23.7 months), despite substantial crossover from dexamethasone to bortezomib.⁶⁷

Based on these phase II-III trials, the toxicity profile of the drug is well defined. The most frequent side effects are gastrointestinal symptoms, which are usually mild. Bortezomib is not myelotoxic but induces rapidly reversible thrombocytopenia (40%-60% decrease in the platelet count). It does not increase the risk of deep vein thrombosis.⁶⁸ Peripheral neuropathy is observed in 30%-40% of cases (grade 3 or 4 in 10%-15%).^{61,69} Signs and symptoms are reversible in 2 of 3 cases after dose reduction or drug discontinuation.⁶⁹ The risk of peripheral neuropathy has justified guidelines for dose reductions. Bortezomib appears to be as effective in older patients⁷⁰ and can be prescribed safely in patients with renal failure,⁷¹ even in patients on dialysis.⁷²

Preclinical studies showed synergy between bortezomib and dexamethasone or cytotoxic agents including alkylating agents and anthracyclines. Therefore, bortezomib was rapidly combined with dexamethasone or cytotoxic agents in clinical trials.⁴⁷ A large randomized phase III trial has shown the superiority of bortezomib plus pegylated liposomal doxorubicin compared with bortezomib alone in terms of TTP.⁷³ Based on these aggregated results, many physicians currently use bortezomib in combination with at least dexamethasone for the treatment of relapsed MM.

Lenalidomide

Lenalidomide is a thalidomide analogue with comparable modes of action but with a more potent *in vitro* efficacy.^{48,50} Clinical development has been rapid as well. After the phase I study, it became apparent that the toxicity profile of lenalidomide was completely different.⁷⁴ Constipation, somnolence, fatigue, and instances of peripheral neuropathy that were frequent with thalidomide were rarely observed. The most frequent side effect was

myelosuppression, mostly after 28 days. In phase II trials, the drug was administered orally for 21 consecutive days.^{54,55} In heavily pretreated patients, response rate was approximately 25% and was further increased by the addition of dexamethasone. Therefore, for subsequent clinical development, lenalidomide (at a dose of 25 mg/day for 21 days in 28-day cycles) was combined with dexamethasone. Two large randomized trials with a similar design were conducted in the United States and Europe.^{75,76} They both showed the superiority of this combination compared with dexamethasone plus placebo, in terms of response rate, TTP, and OS.

Based on these results, lenalidomide was approved for the treatment of relapsed MM both in the United States and Europe. Subsequent analysis of these large randomized studies showed that lenalidomide/dexamethasone was very effective for first relapses, with 67% response rate and 40% CR plus very good partial response (VGPR)⁷⁷ and that the combination was superior to dexamethasone regardless of thalidomide exposure but was more effective in thalidomide-naïve patients than in thalidomide-exposed patients.⁷⁸

The most common high-grade toxicity in phase II-III trials is myelosuppression, and neutropenia is the most frequent hematologic adverse event. However, with dose reductions and growth factors if necessary, the percentage of patients discontinuing lenalidomide because of myelosuppression is very low.⁷⁹ As with thalidomide, single-agent lenalidomide does not increase the risk of deep vein thrombosis, but the combination with high-dose dexamethasone increases this risk and justifies prophylaxis, at least with low-dose acetylsalicylic acid. This drug should be used with caution in patients with renal dysfunction.⁸⁰ Because it is mostly eliminated by the kidney, myelotoxicity (especially thrombocytopenia) is higher in patients with < 50 mL/min creatinine clearance. However, with appropriate dose adjustments, lenalidomide is effective and well tolerated in patients with mild or moderate renal impairment.⁸¹ Finally, although teratogenicity has not been clearly demonstrated, programs for avoiding exposure in women of childbearing potential are justified as well.

Lenalidomide has also been used in combination with both alkylating agents and anthracyclines,⁴⁷ but in the absence of randomized trials the benefit as regards efficacy/toxicity ratio compared with lenalidomide/dexamethasone is unclear.

Combination of Novel Agents

Because the toxicity profile of these agents is different, it appeared logical to combine them with the objective of increasing efficacy without increasing toxicity. Moreover, combination of an IMiD (thalidomide or lenalidomide) with bortezomib was attractive because of a possible synergy of agents having different modes of action. Thalidomide and bortezomib have been combined with either dexamethasone (VTD) or melphalan/prednisone (VMPT), with promising results and an acceptable toxicity.^{82,83} However, because both agents may induce neurologic toxicity, the combination of lenalidomide, which has almost no neurologic toxicity with either thalidomide plus melphalan/prednisone⁸⁴ or with bortezomib, could be even more attractive.⁸⁵ However, in the absence of a randomized study, the benefit of these more complex combinations compared with standard approaches is unknown, especially regarding the efficacy/toxicity ratio.

Table 2A Randomized Studies on Novel Agents in Relapsed Multiple Myeloma

Patient Characteristics	Bortezomib			
	Richardson et al ^{65,67}		Orlowski et al ⁷³	
	Bortezomib 1.3 mg/m ² on Days 1, 4, 8, 11	Dexamethasone 40 mg on Days 1-4, 9-12, 17-20	Bortezomib 1.3 mg/m ² on Days 1, 4, 8, 11	Bortezomib 1.3 mg/m ² on Days 1, 4, 8, 11 Plus PLD 30 g/mL Day 4
Number of Patients	331	336	322	324
Efficacy				
Response rate, %	43	18	41	44
Median TTP, months	62	3.5	6.5	9.3
Median DOR, months	7.8	5.6	7	10.2
Median OS, months	29.8	23.7	65% at 15 months	76% at 15 months
Age, Years	62	61	62	61
Interval Since Diagnosis	3.5 years	3.1 years	37.5 months	35.2 months
Number of Previous Treatments ≥ 2	2 (median)	2 (median)	66%	66%
Toxicity, %				
Grade 3/4 AEs	75	60	64	80
Grade 3/4 neutropenia	14	1	14	30
Grade 3/4 thrombocytopenia	30	6	15	22
Peripheral neuropathy (including grade ≥ 3)	36 (9)	< 1	39 (9)	35 (4)
Deep vein thrombosis	NA	NA	1	1

Abbreviations: AE = adverse event; DOR = duration of response; NA = not available; NR = not reached; OS = overall survival; PLD = pegylated liposomal doxorubicin; TTP = time to progression

Summary

During this 10-year period, the successive introduction of thalidomide, bortezomib, and lenalidomide has offered new salvage possibilities at the time of relapse or in refractory patients (Table 2). This translated into a significant prolongation of OS after relapse for patients relapsing after 2000 and having access to one or more of these agents compared with patients relapsing before 2000.⁸⁶ More generally, the OS of patients diagnosed after 2000 was significantly longer (44.8 months vs. 29.9 months).⁸⁶

Novel Agents for First-line Therapy Younger Patients Eligible for Stem Cell Transplantation

Autologous Stem Cell Transplantation. In 2000, HDT/autologous stem cell transplantation (ASCT) was the standard frontline therapy for patients with newly diagnosed MM up to the age of 65 years and without severe comorbidities.⁸⁷ This strategy has been based on a number of randomized trials, showing a benefit compared with conventional chemotherapy, at least in terms of response rate and progression-free survival (PFS),^{87,88} and in some trials in terms of OS as well.^{89,90} The superiority of HDT/ASCT compared with conventional chemotherapy was mostly because of a better quality of response, with more CR or VGPR. Overall, with HDT/ASCT, the CR plus VGPR rates were 40%-50%, the median PFS was 24-36 months and the median OS was 5-6 years.⁸⁷

The benefit of an even more aggressive strategy with double ASCT, as pioneered by the Arkansas group, remained more controversial. In randomized trials, double ASCT improved the PFS compared with single ASCT⁹¹⁻⁹³ but without OS improvement in two

studies.^{92,93} Moreover, only patients who were not at least in VGPR after 1 ASCT appeared to benefit from the second.^{91,92} Finally, patients with poor-risk cytogenetic abnormalities still did poorly even with double HDT/ASCT.^{37,94} It appeared then that the benefit of a strategy based on further intensification was limited and novel agents were rapidly integrated in the HDT/ASCT paradigm.

Novel Agents as Induction Therapy Before High-Dose Therapy/ASCT

The potential objectives of induction therapy before ASCT are (1) to reduce tumor burden and to increase the post ASCT CR/VGPR rate; and (2) to decrease the plasma cell bone marrow infiltration (in vivo purging).

Before the era of novel therapies, the standard induction was dexamethasone based, either dexamethasone alone or mostly vincristine/doxorubicin/dexamethasone (VAD). Although high-dose dexamethasone induced adverse events, including infections, these regimens were preferred to melphalan/prednisone-based regimens because of a better quality of stem cell collection. However, the CR/VGPR rates after 3-4 cycles remained low (< 10% CR and < 20% CR plus VGPR).

All studies comparing dexamethasone or VAD to induction treatment with thalidomide or bortezomib have shown a superiority of the recent combinations⁹⁵⁻¹⁰¹ and VAD should no longer be considered the standard induction treatment before HDT/ASCT.

Double Combinations. All three novel agents have been tested in combination with dexamethasone. Results are shown in Table 3. With thalidomide/dexamethasone (TD), although the postinduc-

Table 2B Randomized Studies on Novel Agents in Relapsed Multiple Myeloma

Patient Characteristics	Lenalidomide			
	Weber et al ⁷⁵		Dimopoulos et al ⁷⁶	
	Lenalidomide 25 mg/d on Days 1-21 Plus Dexamethasone 40 mg on Days 1-4, 9-12, 17-20	Placebo Plus Dexamethasone 40 mg on Days 1-4, 9-12, 17-20	Lenalidomide 25 mg/d on Days 1-21 Plus Dexamethasone 40 mg on Days 1-4, 9-12, 17-20 (First 4 Cycles)	Placebo, Dexamethasone 40 mg on Days 1-4, 9-12, 17-20 (First 4 Cycles)
Number of Patients	177	176	176	175
Efficacy				
Response rate, %	61	20	60	24
Median TTP, months	11.1	4.7	11.3	4.7
Median DOR, months	15.8	5.1	16.5	7.9
Median OS, months	29.6	20.2	NR	20.6
Age, Years	64	62	63	64
Interval Since Diagnosis	3.1 years	3.1 years	3-4 years	4 years
Number of Previous Treatments ≥ 2	62%	62%	68%	67%
Toxicity, %				
Grade 3/4 AEs	85	20	NA	NA
Grade 3/4 neutropenia	41	4.5	29.5	2
Grade 3/4 thrombocytopenia	15	7	11	6
Peripheral neuropathy	2	1	2	0
Deep vein thrombosis	12	3	11	5

Abbreviations: AE = adverse event; DOR = duration of response; NA = not available; NR = not reached; OS = overall survival; PLD = pegylated liposomal doxorubicin; TTP = time to progression

tion overall response rate was superior to dexamethasone alone or to VAD, the postinduction CR or the post-HDT/ASCT CR plus VGPR rate was not significantly increased.⁹⁵⁻⁹⁷

With bortezomib/dexamethasone (VD), the CR plus VGPR rate is significantly increased compared with VAD, both before and after HDT/ASCT.⁹⁸

With lenalidomide/dexamethasone, in only 1 randomized study the response rate after 4 cycles of induction therapy is available.¹⁰² In this study, CR plus VGPR rate is superior with lenalidomide plus high-dose dexamethasone compared with low-dose dexamethasone. Lenalidomide/dexamethasone has not yet been compared with other induction regimens.

Triple Combinations. Thalidomide or bortezomib have been combined with dexamethasone and a third drug: cyclophosphamide,^{100,103} anthracycline,^{99,101} or together (VTD).¹⁰⁴⁻¹⁰⁶ Results achieved with these combinations are presented in Table 4. Three-drug combinations appeared to be more effective than 2-drug combinations and yielded CR plus VGPR rates of 32%-62% before HDT/ASCT and up to 49%-76% after HDT/ASCT. In three randomized studies, the 3-drug combination of bortezomib/thalidomide/dexamethasone (VTD) was significantly superior to TD^{102,105} and VD¹⁰⁶ in terms of CR or CR/VGPR rates.

Although no randomized study has compared 3-drug combinations, the most effective appears to be the combination containing 2 novel agents (VTD). The addition of a fourth agent does not apparently increase further the efficacy and may increase toxicity.^{107,108}

Table 3 Induction Therapy With Novel Agents Before ASCT: Two-Drug Combinations (Comparative Studies)

Response Measure	VAD ⁹⁶⁻¹⁰¹	TD ^{99,100,104,105}	VD ⁹⁸	RD ¹⁰²	Rd ¹⁰²
Post Induction, %					
CR	2-9	7-14	6	—	—
$\geq$ VGPR	15-17	26-35	39	42	24
$\geq$ PR	54-65	62-76	82	79	68
Post ASCT, %					
CR	9-14	33-37	16	NA	NA
$\geq$ VGPR	32-44	44-64	54	NA	NA

Abbreviations: ASCT = autologous stem cell transplantation; CR = complete response; PR = partial response; RD = lenalidomide/high-dose dexamethasone; Rd = lenalidomide/low-dose dexamethasone; VAD = vincristine/doxorubicin/dexamethasone; VD = bortezomib/dexamethasone; VGPR = very good partial response

Safety of Induction Treatments With Novel Agents. The first issue is feasibility of stem-cell collection. In randomized trials comparing TD or VD and VAD, the number of CD34⁺ cells was superior in the VAD groups, but without significant clinical consequence (proportion of collection failures or time to post-ASCT hematopoietic recovery).^{98,109} With lenalidomide/dexamethasone, stem cell collection is less easy, because of the myelosuppressive effect of lenalidomide, and should be performed early and after cyclophosphamide plus granulocyte colony-stimulating factor

Table 4 Induction Therapy With Novel Therapies Before ASCT: Three-Drug Combinations

Response Measure	Thalidomide-Based		Bortezomib-Based		VTD		
	TAD vs. VAD	TCD vs. c-VAD	BCD	PAD vs. VAD	VTD vs. TD	VTD vs. TD	VTD vs. VD
	Lokhorst et al ⁹⁹	Morgan et al ¹⁰⁰	Einsele et al ¹⁰³	Sonneveld et al ¹⁰¹	Cavo et al ¹⁰⁴	Rosinol et al ¹⁰⁵	Harousseau et al ¹⁰⁶
Number of Patients	402	251	300	300	460	299	482
Post Induction							
CR or CR/nCR	—	19% vs. 9%	10%	—	—	—	14% vs. 12%
≥ VGPR	32% vs. 15%	29% vs. 27%	—	42% vs. 15%	62% vs. 29%	29% vs. 25%	50% vs. 36%
≥ PR	72% vs. 54%	—	84%	83% vs. 59%	94% vs. 79%	82% vs. 75%	90% vs. 81%
Post ASCT							
CR	16% vs. 11%	51% vs. 40%	—	23% vs. 9%	43% vs. 23%	59% vs. 48%	20% vs. 26%
≥ VGPR	49% vs. 32%	67% vs. 43%	—	55% vs. 50%	76% vs. 58%	—	66% vs. 54%

Abbreviations: ASCT = autologous stem cell transplantation; BCD = bortezomib/cyclophosphamide/dexamethasone; c-VAD = cyclophosphamide/vincristine/doxorubicin/dexamethasone; CR = complete response; nCR = near complete response; PAD = bortezomib/doxorubicin/dexamethasone; TAD = thalidomide/doxorubicin/dexamethasone; TD = thalidomide/dexamethasone; VAD = vincristine/doxorubicin/dexamethasone; VD = bortezomib/dexamethasone; VGPR = very good partial response; VTD = bortezomib/thalidomide/dexamethasone

(G-CSF) priming or in some cases priming with G-CSF plus plerixafor.^{110,111}

Thalidomide and lenalidomide may increase the risk of deep vein thrombosis when they are used in combination with dexamethasone, and especially for induction treatment because the tumor burden is higher. Therefore, some form of prophylaxis is justified, at least acetylsalicylic acid or low-molecular-weight heparin in patients at higher risk.

Thalidomide and bortezomib are associated with peripheral neuropathy. However, with thalidomide the risk is related to cumulative dose and is limited with short treatment (3-4 months). With bortezomib, peripheral neuropathy may occur rapidly and in studies on bortezomib-containing induction treatments, the incidence of grade > 1 and grade > 2 peripheral neuropathy was, respectively, 25%-30% and 7%-15%.^{98,104,105} Reduced doses of bortezomib (1 mg/m² instead of 1.3 mg/m²) in combination with thalidomide and dexamethasone (VTD) were more active and less neurotoxic than conventional doses of bortezomib plus dexamethasone.¹⁰⁶

Will the Better CR Rate Achieved With Novel Induction Regimens Translate Into Longer PFS? In the context of HDT/ASCT, the prognostic impact of achieving CR or at least VGPR has been clearly demonstrated.^{112,113} Therefore, one can hope that the better post HDT/ASCT CR or CR/VGPR achieved with novel agents will translate into longer PFS. However, in most randomized trials addressing the question of induction therapy, it will be difficult to answer this question because post HDT/ASCT treatment was not the same in the two induction groups. In IFM 2005-01, post HDT/ASCT maintenance was comparable in the VAD and VD arms. Median PFS was 36 months in the VD arm versus 30 months in the VAD arm ($P = .057$ without significant benefit in OS).⁹⁸

An indirect way to address this question is to look at the prognostic effect of achieving CR/VGPR after induction treatment. In the past, it has been very difficult to show that it was better to achieve CR before HDT/ASCT than after, mostly because CR was a rare event.¹¹³ While the IFM group failed to show a benefit of achieving CR after VAD induction therapy,¹¹² the Spanish group showed a trend in favor of a better outcome in patients achieving CR before

HDT/ASCT.¹¹⁴ In the IFM 2005-01 trial, because the CR/VGPR rate was improved in the VD arm, it was possible to demonstrate that patients achieving at least VGPR after induction therapy had a significantly longer PFS than patients having less than VGPR or even than patients achieving PR.¹¹⁵

High-Dose Therapy Regimen

Until now the standard high-dose therapy regimen has been melphalan intravenous (I.V.) 200 mg/m², which is superior to melphalan 140 mg/m² plus total-body irradiation¹¹⁶ and to melphalan 100 mg/m².¹¹⁷ Attempts to improve results by adding another cytotoxic agent have not been convincing because of higher toxicity. Recently, the addition of bortezomib to high-dose melphalan yielded promising results. In a phase II study from the IFM group, 70% of patients achieved at least VGPR after ASCT and a matched-controlled analysis suggested that this combination was superior to melphalan 200 mg/m².¹¹⁸

Post-ASCT Therapy

Before the year 2000, almost all patients ultimately relapsed even after HDT/ASCT. The role of maintenance therapy is to increase remission duration by controlling the malignant clone. This concept has been developed in the past with interferon (IFN)- α ¹¹⁹ but the benefit was not considered sufficient to justify the cost and toxicity of a prolonged treatment with IFN. In the context of HDT/ASCT, a randomized study failed to show any improvement of the outcome with IFN maintenance.¹²⁰ The concept of maintenance therapy has been revisited with novel agents.

Maintenance With Thalidomide. Thalidomide has been tested in this setting by several groups. Five randomized studies have been completed and are summarized in Table 5.¹²¹⁻¹²⁷ Although the study design and the dose and duration of thalidomide treatment were variable, all studies showed a significant benefit in terms of CR (or CR plus VGPR) rate and PFS. However, OS was significantly prolonged in only 2 of 5 studies, because of a shorter OS after relapse in the thalidomide groups. This might be explained by the fact that more patients received thalidomide as salvage treatment in

Table 5 Maintenance Therapy after Autologous Stem Cell Transplantation: Randomized Studies

Study Characteristic	Attal et al ¹²¹	Barlogie et al ¹²²	Spencer et al ¹²³	Lokhorst et al ¹²⁴	Morgan et al ^{125,127}
Number of Patients	597	668	269	556	NA
Induction	No thalidomide	Thalidomide 50%	No thalidomide	50% thalidomide	50% thalidomide
ASCT	Double	Double	Single	Double	Single
Thalidomide Administration	Starting dose 400 mg/day until relapse	Starting dose 400 mg/day until relapse	200 mg/day 1 year	200 mg/day until relapse	100 mg/day until relapse
Date of Randomization	After ASCT (if no progression)	Initial	After ASCT (if no progression)	Initial	After ASCT
Randomization	No treatment vs. pamidronate vs. thalidomide + pamidronate	Thalidomide vs. no thalidomide	Thalidomide/prednisone vs. prednisone	TAD → thalidomide VAD → IFN	Thalidomide vs. no thalidomide
Median Follow-up	40 months	42 months	33 months	52 months	32 months
Complete Response Rate	67% vs. 57% or 55% ^a <i>P</i> = .03	62% vs. 43% <i>P</i> < .001	65% vs. 44% ^a <i>P</i> < .001	66% vs. 54% ^a <i>P</i> = .005	NA
PFS of EFS	3-year, 52% vs. 37% <i>P</i> = .002	5-year, 56% vs. 44% <i>P</i> = .01	3-year, 42% vs. 23% <i>P</i> < .001	Median 3 months vs. 22 months <i>P</i> < .001	Better in patients with < VGPR <i>P</i> < .007
OS	4-year, 87% vs. 75% <i>P</i> = .04	5-year, 65% vs. 65% NS	3-year, 26% vs. 75% <i>P</i> = .004	73 months vs. 60 months <i>P</i> = .77	NS
	—	Updated analysis 8-year 57% vs. 44% <i>P</i> = .09 ^{b,126}	—	—	

^aCR + VGPR.^bSignificant in patients with cytogenetic abnormalities.

Abbreviations: ASCT = autologous stem cell transplantation; CR = complete response; EFS = event-free survival; IFN = interferon; NA = not available; OS = overall survival; PFS = progression-free survival; TAD = thalidomide/doxorubicin/dexamethasone; VAD = vincristine/doxorubicin/dexamethasone; VGPR = very good partial response

the no maintenance arm. It should be noted that at the time these studies were completed bortezomib and lenalidomide were less used than now. With more effective salvage therapies at relapse, OS might become correlated with first remission duration and differences in OS might appear later.¹²⁶

Therefore, although post-ASCT treatment with thalidomide appears to improve the outcome, the drug has never been approved in this indication because a number of questions still persist: (1) what is the recommended daily dosage? and (2) what is the optimal duration of treatment? Prolonged treatment with thalidomide increases the risk of severe peripheral neuropathy and might select resistant clones and reduce the efficacy of salvage treatment at relapse. Actually, in 2 studies a large proportion of patients had to discontinue their treatment because of adverse events (mostly peripheral neuropathy and fatigue).^{121,122} Do all patients benefit from maintenance therapy, and especially patients with poor-risk cytogenetics? In the Arkansas group study, with long-term follow-up, it appeared that patients with translocations by conventional cytogenetics had a better OS in the thalidomide group.¹²⁶ On the other hand, the British group suggests that OS might be shorter in the thalidomide group for patients with del(17p).¹²⁷

Maintenance With Other Novel Agents. Lenalidomide appears to be a better drug than thalidomide for long-term maintenance treatment because it is much better tolerated and, particularly, induces peripheral neuropathy very rarely. Two randomized studies (from the Cancer and Leukemia Group B [CALGB] and from

Table 6 Maintenance Therapy With Low-Dose Lenalidomide After ASCT Randomized Studies

Study Characteristic	CALGB 100104 McCarthy et al ¹²⁸	IFM 2005-02 Attal et al ¹²⁹
Inclusion Criteria	< 70 years SD or better ≤ 1 year from treatment initiation	< 65 years SD or better ≤ 6 months after frontline ASCT
Consolidation	—	Lenalidomide 25 mg/day
Randomization	Lenalidomide 10 mg/day vs. placebo until progression	Lenalidomide 10-15 mg/day vs. placebo until progression
Number of Patients	418	614
Median Follow-up	12 months	24 months
TTP/PFS	Not reached vs. 25.5 months HR, 0.42	PFS median not reached vs. 24 months HR, 0.46
OS	NS	NS

Abbreviations: ASCT = autologous stem cell transplantation; HR = hazard ratio; OS = overall survival; PFS = progression-free survival; SD = stable disease; TTP = time to progression

the Intergroupe Francophone du Myelome [IFM]) have compared low-dose lenalidomide or placebo until progression as post HDT/ASCT maintenance therapy.^{128,129} Designs of these two studies are quite comparable, except the fact that in the IFM study all patients received a consolidation with full-dose lenalidomide after ASCT.

Table 7 MP Versus MPT: Patient Characteristics and MPT Regimens From Randomized Studies

Characteristic	GIMEMA ^{144,145}	IFM 99-06 ¹⁴⁶	IFM 01-01 ¹⁴⁷	HOVON ¹⁴⁸	NMSG ¹⁴⁹
Number of Patients (MPT)	331 ¹⁶⁷	447 ¹¹³	232 ¹¹³	333 ¹⁶⁵	357 ¹⁸²
Median Age, Years (Range)	72 (60-85)	69 (65-75)	78.5 (75-89)	72 (NA)	74.5 (mean; 49-92)
WHO 3/4, %	5	8	7	4	30
MPT Regimen					
Number of cycles	6	12	12	Until plateau	Until plateau
Melphalan dosing	4 mg/m ² days 1-7	0.25 mg/kg days 1-4	0.2 mg/kg days 1-4	0.25 mg/kg days 1-5	0.25 mg/kg days 1-4
Thalidomide dosing	100	Up to 400	100	200	Up to 400
Maintenance	Yes	No	No	Yes	Yes

Abbreviations: MP = melphalan/prednisone; MPT = melphalan/prednisone/thalidomide; NA = not available; WHO = World Health Organization

Table 8 MP Versus MPT: Results From Randomized Studies

Response Rate, %	GIMEMA ^{144,145}	IFM 99-06 ¹⁴⁶	IFM 01-01 ¹⁴⁷	HOVON ¹⁴⁸	NMSG ¹⁴⁹
Overall (≥ PR)					
MP	48	35	31	45	40
MPT	69	76	62	66	57
PValue	< .0001	< .0001	< .001	< .001	< .0001
≥ VGPR					
MP	11	7	7	10	7
MPT	29	47	21	27	23
PValue	< .0001	< .0001	< .001	< .001	< .0001
Median PFS, Months					
MP	14.5	18	18.5	9	14
MPT	21.8	27.5	24	13	15
PValue	.0004	< .0001	.001	< .001	NS
Median OS, Months					
MP	47.6	33	29	32	32
MPT	45	51.5	44	40	29
PValue	NS	.006	.028	.05	NS

Abbreviations: MP = melphalan/prednisone; MPT = melphalan/prednisone/thalidomide; NS = not significant; OS = overall survival; PFS = progression-free survival; PR = partial response; VGPR = very good partial response

Preliminary results are in Table 6: in both studies lenalidomide maintenance dramatically improved PFS or TTP. Until now this benefit does not have translated into prolonged OS. An important finding from these two trials is that lenalidomide appears to prolong PFS across all prognostic subgroups defined for stratifying randomization (type of induction treatment and status at transplantation, β 2M level, chromosome 13 deletion by FISH).

Bortezomib every 2 weeks has also been evaluated as maintenance after HDT/ASCT by the Dutch group, but results are not yet available.¹⁰¹

Novel Agents Before and After High-Dose Therapy/ASCT

A number of groups are evaluating novel therapies both before and after HDT/ASCT, but the only mature results come from the Arkansas group investigators. They have integrated novel agents in their complex approach including tandem ASCT called total

therapy programs. In the Total Therapy 2 program, patients were randomly assigned to receive thalidomide throughout their treatment. Thalidomide appeared to increase the response rate, PFS, and long-term OS.^{122,126} More recently, in the Total Therapy 3 program the same group has added bortezomib to induction and consolidation. Current results show an impressive CR rate of > 90% and 5-year PFS and OS rates of 71% and 78%.^{130,131} The addition of bortezomib appears to partially overcome the poor prognosis related to t(4;14) and del(17p).^{131,132} These results appear to be the best ever achieved in MM. Whether such a complex and potentially toxic strategy is needed in all patients will be clarified by the recently completed trials.

Allogeneic Stem Cell Transplantation. Allogeneic stem cell transplantation (SCT) following myeloablative conditioning regimen can induce molecular remissions and before the era of novel thera-

Table 9 MP Versus MPV: Results of the VISTA Randomized Trial^{151,152}

Treatment	Number of Patients	Response Rate	CR Rate	Median TTP	Median TNT	Median TFI	3-Year OS
MP	331	35%	4%	16.6 months	19.2 months	8.4 months	54%
MPV	337	71%	30%	24 months	28.1 months	17.6 months	68.5%
P Value	—	< .001	< .001	< .001	< .001	< .001	.0008

Abbreviations: CR = complete response; MP = melphalan/prednisone; MPV = melphalan/prednisone/bortezomib; OS = overall survival; TFI = treatment-free interval; TNT = time to next treatment; TTP = time to progression

Table 10 Results of Randomized Studies of Dexamethasone-Based Combinations

Study	Number of Patients	Median Age, Years	Response Rate	≥ VGPR Rate	Median PFS	Median OS
Ludwig et al¹⁵⁵						
MP	143	72	50%	13%	20.7 months	49.4%
TD	145	72	68%	26%	16.7 months	41.5%
P value	—	—	.002	.006	.10	.024
Rajkumar et al¹⁰²						
RD	224	66 ^a	81%	50%	19.1 months	1-year 87%
Rd	223	65 ^b	70%	40%	25.3 months	1-year 96%
P value	—	—	.009	.04	.026	.0002

^a53% > 65 years of age.

^b51% > 65 years of age.

Abbreviations: MP = melphalan/prednisone; RD = lenalidomide/high-dose dexamethasone; Rd = lenalidomide/low-dose dexamethasone; TD = thalidomide/dexamethasone; VGPR = very good partial response

pies was the only therapy with a potential for cure or long-term disease control in at least some patients.¹³³ However toxicity is excessively high with transplant-related mortality of up to 50% in some studies. Therefore, myeloablative conditioning is abandoned by a large majority of investigators.

Much of the clinical effect of allogeneic SCT has been attributed to the immunologic effect of donor lymphoid cells, the so-called graft-versus-myeloma (GVM) effect. This antitumor effect of donor cells, which is unfortunately linked to graft-versus-host-disease (GVHD), is the basis of reduced-intensity conditioning (RIC) allogeneic SCT. The principle of RIC allogeneic SCT is to reduce transplantation-related toxicity while harnessing the GVM effect. Preliminary experience showed that RIC allogeneic SCT is feasible in MM even in patients > 60 years of age and with matched-unrelated donors.¹³⁴ However, in patients with a high tumor burden, the allogeneic GVM is not sufficient and relapses are more frequent than with standard myeloablative regimens.¹³⁵ Therefore RIC allogeneic SCT is mostly performed after HDT/ASCT. The Seattle group recently updated their results with this approach¹³⁶ and reported 5-year PFS and OS of, respectively, 36% and 64%. However, toxicity remained high with 11% transplantation-related mortality, 42% grades 2–4 acute GVHD, and 72% chronic GVHD. Three studies have prospectively compared tandem ASCT-RIC allotransplantation with double ASCT.^{137–139} The Italian study is the only one to show a significant benefit in favor of RIC allogeneic SCT. Even in this study, an updated analysis shows that median PFS is only 37 months, because of both toxic deaths and relapses.¹⁴⁰ Considering the results currently achieved with novel agents with or without ASCT, this strategy should not be proposed in the up-front setting except in selected patients with very-poor-risk features. The

best indication for RIC allogeneic SCT appears to be responsive to relapses, within a clinical trial. The most attractive clinical research area is the evaluation of novel agents after RIC allogeneic SCT with the objective of upgrading the level of remission.¹⁴¹

Elderly Patients

Although the introduction of HDT supported by ASCT has markedly increased the PFS and OS in younger patients, during the past four decades there has been almost no improvement in the prognosis of elderly patients with MM.¹⁴² Until recently, the standard of care has been the combination of melphalan and prednisone (MP).¹⁴³

The introduction of the three novel agents thalidomide, bortezomib, and more recently lenalidomide, in the first-line therapy of elderly patients has dramatically improved outcome and is completely changing the management of MM in elderly patients.

Novel agents have been added to the treatment of elderly patients in 3 different ways: (1) addition of 1 novel agent to the MP combination, (2) addition of 1 novel agent to dexamethasone, (3) maintenance therapy after induction treatment.

Melphalan/Prednisone–Based Combinations. The first novel agent to be combined with MP has been thalidomide. Currently, 5 randomized studies comparing MP and MP/thalidomide (MPT) as primary treatment in elderly patients with MM have been published.^{144–149}

The inclusion criteria, design of the studies, and dose of chemotherapy and of thalidomide have varied (Table 7). However, results are quite reproducible. They can be summarized as follows (Table 8): response rates, either at least partial response or at least VGPR have been significantly increased in the MPT arms in 5 of 5 studies; PFS has been significantly improved in 4 of 5 studies; and

OS has been significantly improved in 3 of 5 studies. OS partly depends on the efficacy of salvage treatment after progression and on the availability of novel agents for relapse management.

As a consequence of these studies the regimen MPT is now considered a new standard of care and it has been approved by the European Medicines Agency (EMA) for the treatment of patients with newly diagnosed MM over the age of 65 years. However, safety may be a concern especially in very old or frail patients. As an example, in the Nordic trial, the median age was 78 and the proportion of patients with an Eastern Cooperative Oncology Group (ECOG) performance status (PS) > 2 was 30%.¹⁴⁹ This high incidence of more frail patients induced a high toxic death rate (mostly in patients over 75 years of age) and a lower compliance to treatment. As a consequence, PFS was not improved in the MPT arm. One might speculate whether higher doses of melphalan (0.25 mg/kg/day for 4 days every 6 weeks) and of thalidomide (200 mg/day 1 week and up to 400 mg/day) and inclusion of older and more frail patients explain that a better response rate does not translate into a longer PFS in the MPT arm.¹⁴⁹

Conversely, in the French trial on patients over 75 years of age, doses of melphalan and thalidomide were lower (0.2 mg/kg/day and 100 mg/day, respectively) and MPT was significantly superior to MP both for response rates and for PFS.¹⁴⁷

The second agent to be combined with MP has been bortezomib. Following encouraging data from a phase I/II trial on the combination MP plus bortezomib (MPV),¹⁵⁰ the large randomized VISTA trial has compared MP and MPV.¹⁵¹ Results were recently updated¹⁵² and are summarized in Table 9. MPV was significantly superior to MP for all parameters measuring response and outcome. An important finding is that the CR rate was 30%, quite comparable to that achieved with HDT in younger patients. Therefore, MPV is also a new EMA-approved standard of care in elderly patients.

However, while results were not significantly impaired in patients over 75 years of age, safety was also a concern in this trial. In the MPV arm, the incidence of grade 3/4 peripheral sensory neuropathy was 14% and 30% of patients had to discontinue their treatment or least bortezomib because of treatment-related adverse events.¹⁵¹

Lenalidomide has also been associated with MP (MPR regimen). Though the phase I/II study has yielded encouraging results,¹⁵³ preliminary analysis of a randomized trial comparing MP, MPR, and MPR/lenalidomide maintenance failed to show an improved PFS in the MPR arm compared with MP, despite a higher response rate.¹⁵⁴ This might be again explained by a higher myelotoxicity and a lower compliance in patients over 75 years of age.

Dexamethasone-Based Combination. The combination of thalidomide with dexamethasone (TD) has been widely used as primary therapy in MM. This combination was compared with MP in a randomized study in elderly patients.¹⁵⁵ While the response rate including CR rate was superior in the TD arm, there was no benefit in terms of PFS and OS was significantly shorter in the TD arm, particularly in patients over 75 years of age (Table 10). This was explained by a higher toxicity and a lower compliance in the TD arm. In this study, both the dose of thalidomide (50-400 mg/day) and the dose of dexamethasone (4-days blocks at 40 mg/day) were probably too high in patients older than 75 years or with poor PS,

which might explain the high incidence of early deaths due to infections or cardiac complications.

The optimal dose of dexamethasone to be combined with IMiDs in first-line therapy for MM was the purpose of a randomized study recently published by the ECOG comparing lenalidomide plus high-dose dexamethasone (40 mg for 4 consecutive days 3 times per month) versus lenalidomide plus low-dose dexamethasone (40 mg weekly).¹⁰² Again, while the response rate was superior with high-dose dexamethasone, median PFS and 1-year survival were significantly longer in the low-dose arm (Table 10), because of a higher toxicity in the high-dose dexamethasone arm. The incidence of any grade 3/4 adverse events was 52% in the high-dose dexamethasone arm versus 35% in the low-dose dexamethasone arm. As a consequence there were more early deaths (5% vs. 1%) and more treatment discontinuations because of adverse events (27% vs. 19%) in the high-dose dexamethasone arm. This was particularly the case in patients over the age of 70 years because the median duration of treatment was 9.7 months in the low-dose dexamethasone arm versus only 3.8 months in the high-dose dexamethasone arm, which might explain why median PFS and 3-year OS were superior in the low-dose arm.¹⁵⁶ Therefore, lenalidomide plus low-dose dexamethasone might be another standard of care in elderly patients and is currently compared with MPT in an ongoing randomized trial.

Maintenance Therapy. With MPT primary therapy, there is no current evidence that thalidomide maintenance further increases PFS, as in none of the randomized trials evaluating MPT was this question specifically addressed. However, it should be noted that, in the two IFM studies, the better PFS translated in an OS benefit despite the absence of maintenance therapy,^{146,147} while in the Italian study MPT induction was followed by a thalidomide maintenance and there was no OS benefit in the MPT due to a shorter survival after relapse.¹⁴⁵

Three recent studies show that maintenance therapy improves response rate or PFS in elderly patients but, to date, no improvement in OS. The most convincing is the MM015 randomized trial, which compared 9 cycles of MP, 9 cycles of MPR, 9 cycles of MPR followed by low-dose lenalidomide maintenance (MPR-R).¹⁵⁴ The MPR-R arm was dramatically superior to the other two in terms of PFS. However, until now there has been no OS benefit in the lenalidomide maintenance arm.

Preliminary analysis of an Italian randomized trial showed that 4-drug induction therapy (MPT plus bortezomib) followed by a maintenance therapy with bortezomib plus thalidomide significantly increased both the response rate and 3-year PFS compared with the new standard regimen MPV.¹⁵⁷ A randomized Spanish study also used maintenance therapy with bortezomib plus thalidomide or bortezomib plus dexamethasone and showed further increase of the CR rate during maintenance (from 25% to 42%).¹⁵⁸ Although these two studies did not directly assess the role of maintenance, they both show that maintenance therapy may improve results achieved by induction treatment.

Summary. The introduction of novel agents in primary therapy for elderly patients has two important consequences: (1) though there had been no significant improvement with conventional

chemotherapy during 4 decades, we now have several possibilities that are significantly superior to MP (MPT, MPV, and MPR followed by lenalidomide maintenance) or appear effective and well tolerated (lenalidomide/low-dose dexamethasone [Rd]); and (2) while patients over 75 years of age were treated with reduced-dose alkylating agents or only with palliative approaches, now they can be treated with effective combinations (MPT, MPV, Rd).

While waiting for results of ongoing randomized trials that compare some of these approaches, it is not possible to determine which of the new standard regimens is best. A number of criteria must be considered when deciding the initial therapy for an elderly patient with symptomatic MM, including patient choice.

Bortezomib-based regimens are preferred in the case of renal failure or previous episode of deep vein thrombosis. IMiD-based regimens are preferred when oral administration is more suitable. Lenalidomide-based regimens are preferred in the case of concomitant peripheral neuropathy, because both thalidomide and bortezomib are potentially neurotoxic.

The key question for treatment decision in elderly patients is actually to evaluate the efficacy/toxicity ratio and to reduce toxicity of these regimens. The issue of the dose is critical and simple guidelines may improve treatment outcome. Dexamethasone: the IFM demonstrated that despite higher response rates, PFS was not superior with dexamethasone-based regimen compared with MP, and that toxicity was greater (infections, diabetes, gastro-intestinal and psychiatric complications.)¹⁵⁹ The conclusion was that high-dose dexamethasone should not be routinely recommended as first-line therapy in elderly patients. Following results of the ECOG randomized trial,¹⁰² dexamethasone should be better used weekly (low-dose dexamethasone) in all elderly patients (at a dose of 40 mg/week up to the age of 70 years, 20 mg/week in patients over 70 years).

In patients over 75 years of age, melphalan should be used at reduced dosage (0.2 mg/kg on 4 consecutive days every 6 weeks) and the dose of thalidomide should not be superior to 100 mg/day.¹⁴⁷ In order to reduce the risk of peripheral neuropathy, which is the most frequent reason for stopping bortezomib treatment, two groups have evaluated a new MPV regimen with weekly instead of biweekly administration of bortezomib.^{158,160} They found that the efficacy was not significantly inferior but that the incidence of severe peripheral neuropathy was dramatically reduced.

Careful monitoring of blood cell counts are mandatory in patients receiving alkylating agents and/or lenalidomide. Before deciding treatment, a geriatric evaluation must be performed in all frail patients, those over the age of 75 years, or in patients with severe comorbidities. In patients for whom geriatric assessment does not show a positive benefit/risk ratio, attenuated-dose treatment (such as low-dose alkylating agents) should be considered.

Supportive Care

Ten years ago, 2 major advances in the field of supportive care had been achieved: bisphosphonates in the prevention of bone disease complications, and erythropoiesis-stimulating agents to prevent the effects of anemia on quality of life and reduce blood transfusions. However, in the past 10 years, some concerns have been raised regarding the use of these agents.

Bisphosphonates in Bone Disease

In order to delay skeletal-related events, bisphosphonates have been widely used for patients with lytic bone lesions.¹⁶¹

Intravenous aminobisphosphonates (pamidronate, zoledronate) were generally preferred because of their more potent in vitro activity and to concerns regarding absorption of oral clodronate. However, with more experience, 2 serious adverse events that had not been previously observed were described: (1) worsening of renal function when zoledronate is used in patients with renal impairment,¹⁶² Although this complication is rare, the product label of pamidronate and zoledronate was updated to include warnings of nephrotoxicity and restrictions for patients with renal impairment; and (2) osteonecrosis of the jaw with long-term use of aminobisphosphonates.^{163,164} This complication initially induced significant morbidity because of delayed diagnosis and lack of effective interventions. The typical presentation is now well known: exposed bone and no healing of soft tissue or no mucosal covering after 6-8 weeks are the major findings. Pain, tissue swelling, and infection are possible. The cause of this osteonecrosis is not fully known and is probably multifactorial. Risk factors have been extensively studied and include the use of zoledronate more than pamidronate, long-term exposure to intravenous bisphosphonates (with an increasing risk after two years of treatment), dental extraction or procedure, infection, and older age. In the absence of effective treatment, preventive measures including detailed dental assessment and preemptive dental care are recommended, and guidelines from different expert panels and scientific societies have been published.^{165,166} The dose of I.V. bisphosphonates in long-term treatment should also be discussed.¹⁶⁷

Erythropoiesis-Stimulating Agents

The effect of erythropoiesis-stimulating agents on the survival of patients with cancer has recently become a matter of discussion. Moreover, the use of these agents might increase the risk of thrombosis in patients treated with IMiDs. Therefore these agents are currently used more cautiously.

Objectives of Myeloma Treatment

The dramatic improvements observed during this 10-year period have also changed the objectives of MM treatment. In the past, the objective of treatment in elderly patients was to achieve any degree of response and to stop treatment when the response was stable (plateau phase). Patients were retreated at the time of symptomatic relapse. Only for younger patients, the objective was more ambitious since it has been shown in studies on HDT/ASCT that CR achievement was associated with longer PFS and/or OS.^{89,90,168}

Effect of Complete Response

In the field of HDT/ASCT, the prognostic effect of CR has actually long been a debated question but it is now accepted that achievement of CR or at least VGPR is associated with better outcome and should be one objective of treatment.^{112,113,169}

However, it is equally clear now that the effect of CR depends on the clinical behavior of the disease. The Arkansas group has suggested that patients with history of previous monoclonal gammopathy or indolent MM might have extended survival without

Table 11 Criteria for Definition of Response

Response Measure	EBMT Criteria ^a ; Blade et al ¹⁷⁸	IMWG Uniform Criteria ^b ; Durie et al ⁶
SCR	ND	CR plus normal FLC ratio Absence of clonal plasma cells by immunochemistry or fluorescence
CR	Absence of M protein in serum and urine by IFX; < 5% bone marrow plasma cells; no increase of lytic bone lesions; disappearance of soft tissue plasmacytomas	Same definition
VGPR	ND	Serum and urine M protein detectable by IFX but not on electrophoresis or 90% or greater reduction in serum M-protein plus urine M-protein < 100 mg/24 h
PR	≥ 50% reduction of serum M protein and reduction in 24-hour urinary M protein by 90% or < 200 mg for nonsecretory MM ≥ 50%, reduction in bone marrow plasma cells, ≥ 50% reduction in the size of soft tissue plasmacytomas	Same definition plus for nonsecretory MM; ≥ 50% decrease in the difference between involved and uninvolved FLC
MR	25%-49% reduction of serum M protein; 50%-89% reduction in 24-h urinary M protein; for nonsecretory MM 25%-49% reduction in bone marrow plasma cells; 25%-49% reduction in the size of soft tissue plasmacytomas	ND
NC or SD	Not meeting criteria for MR or PD	Not meeting criteria for PR or PD
PD	> 25% increase in serum M protein	Same definition plus absolute increase in serum M protein ≥ 0.5 g/dL; absolute increase in urine M protein ≥ 200 mg/h; for nonsecretory MM, increase in the difference between involved and uninvolved FLC > 10 mg/dL
	> 25% increase in 24-hour urinary M protein; > 25% increase in bone marrow plasma cells; > 25% increase in the size of soft tissue plasmacytomas or new bone lesions	—

^aMaintained at least 6 weeks.

^bTwo consecutive assessments before any new therapy.

Abbreviations: CR = complete response; FLC = free light chain; MM = multiple myeloma; MR = minimal response; NC = no change; ND = not defined; PD = progressive disease; PR = partial remission; SCR = stringent CR; SD = stable disease; VGPR = very good partial response

achieving CR,¹⁷⁰ and the IFM group has confirmed that, currently in patients with good-risk MM, CR/VGPR achievement might not be necessary for OS.¹¹² In more indolent MM, it might be possible to obtain long survival without a total disappearance of the M-component. On the contrary, analysis of the intensive programs at Arkansas University suggested that stringently defined CR was critical for EFS and OS only in a small subgroup of patients with poor prognosis, as defined by gene expression profiling.¹⁷¹ And in the IFM experience, achieving at least VGPR was significantly better in patients with poor-risk characteristics defined by ISS stage 3 or by the presence of poor-risk cytogenetic abnormalities t(4;14) and/or del (17p).¹¹² These findings could mean that, in more aggressive MM, which is usually characterized by a more proliferative clone, elimination of this clone is necessary to obtain prolonged response.¹⁷² However, aggressive forms of MM can respond rapidly and completely to intensive treatment but still relapse early.³⁰⁻³⁶ Therefore, CR achievement is not the only objective but maintaining response is important as well. One way to prolong TTP might be to upgrade the level of response. It was already known from the allogeneic transplantation experience that patients achieving molecular remissions had a better outcome.^{173,174} More recently the Spanish group has shown that, in patients treated with HDT/ASCT, achieving an immunophenotypic remission as defined by multiparameter flow cytometry was the most important prognostic factor.¹⁷⁵ It remains to demonstrate that these findings may be reproduced at the multicenter level before accepting this level of remission in clinical practice.

Another important point in this field is that it is now possible to achieve high CR rates as well with novel therapies. Then it became possible to demonstrate the prognostic effect of CR out of the HDT/ASCT paradigm. A subanalysis of the two phase 3 randomized studies on lenalidomide/dexamethasone showed that, even in relapsed patents, achievement of CR with lenalidomide/dexamethasone was associated with longer PFS and OS.¹⁷⁶ The prognostic effect of achieving CR with MPV has also been shown in a subanalysis of the VISTA trial in newly diagnosed patients ineligible for ASCT.¹⁷⁷ Therefore, like in younger patients treated with HDT plus ASCT, the objective of primary therapy in elderly patients should be to achieve CR. However, induction should not be too toxic, otherwise the benefit of a more effective treatment may be hampered by an excessive toxic death rate or by poor compliance to treatment.^{149,155}

Criteria for Response Assessment

As it appeared that the magnitude of response was an important prognostic factor, criteria for response assessment had to be redefined, especially to better define the types of response that were associated with a better outcome. Therefore the EBMT criteria that had been introduced in 1998¹⁷⁸ were modified in order to introduce the concept of near-CR and VGPR, which were put together in the VGPR definition and to introduce serum FLC in the definition of CR (stringent CR). The differences between EBMT and these IMWG uniform criteria are shown in Table 11.

Risk-Adapted Therapy

Until now, there has been no clinical evidence justifying a risk-adapted strategy. For instance, no study has clearly shown which patients should benefit from HDT/ASCT and which patients might be initially treated without intensive treatments. However, novel agents might change this situation. They appear to be effective across different prognostic subgroups and might be useful in patients with poor prognostic characteristics. In the IFM 2005-01 trial, VD was equally effective and significantly superior to VAD across all prognostic subgroups.⁹⁸ Patients with t(4;14) and/or del(17p) had the same response rate than patients without these abnormalities, which is also found in other studies evaluating induction treatment with bortezomib.¹⁰³⁻¹⁰⁵ This better response rate to induction treatment with bortezomib in patients with t(4;14) translates into a longer PFS,¹⁷⁹ indicating that bortezomib might at least partially overcome poor prognosis associated with this cytogenetic abnormality, both in the setting of HDT/ASCT¹³¹ and in elderly patients.¹⁵¹ However, bortezomib does not improve the poor PFS related to del(17).¹⁷⁹ Data with lenalidomide are less clear.¹⁸⁰⁻¹⁸²

Questions for the Near Future

The Place of HDT/ASCT

Results of HDT/ASCT have dramatically improved with the addition of novel agents. Very high CR plus VGPR rates up to 75% are now achieved after induction treatments with novel agents followed by HDT/ASCT. Novel agents after HDT/ASCT may prolong remission and 3-year PFS of 60%-70% might be obtained. But at the same time, first-line therapy with novel agents is markedly improving the outcome in patients who are not candidates for HDT/ASCT or who are not willing to undergo HDT programs. We have already described the dramatic improvement obtained in elderly patients with novel agents in combination with either MP or dexamethasone. Combinations with lenalidomide plus dexamethasone have been evaluated by US investigators as primary therapy both in young patients who did not wish to undergo HDT/ASCT and in older patients. These studies show that treatments with lenalidomide/dexamethasone^{102,183} or more recently with lenalidomide/bortezomib/dexamethasone¹⁸⁴ may also yield very high CR plus VGPR rates and encouraging PFS. Because these treatments are well tolerated, they may be given for long periods of time and it appears that, with prolonged treatment, the response rates continue to improve. Moreover, patients who have not received HDT up-front might receive it at time of relapse. As a consequence the place of HDT/ASCT is again challenged and some investigators are already suggesting that first-line treatment with HDT/ASCT should be abandoned. The only way to determine whether HDT/ASCT plus novel agents is still superior to novel agents without intensive treatments (plus HDT/ASCT at progression/relapse) is to perform randomized trials that are actually ongoing or planned. One important question to be addressed by these studies will be to determine in which subgroups of patients up-front HDT/ASCT is superior and remains necessary.

Curiously, while the place of HDT/ASCT in the management of younger patients is again discussed, a study from Italy shows that incorporating novel agents in the ASCT paradigm might

also yield very good results in older patients. This group used a semi-intensive approach with 2 courses of melphalan 100 mg/m² supported with ASCT. In their initial experience, this approach was superior to MP¹⁸³ but these results were not confirmed by the IFM 9906 trial in patients aged 65-75 years.¹⁴⁶ The same Italian group recently reported on a phase II study in which 102 patients aged 65-75 years received 4 cycles of a bortezomib-based induction followed by 2 courses of melphalan 100 mg/m² and by lenalidomide consolidation/maintenance.¹⁸⁶ The final CR plus VGPR rate was 78% with very encouraging 2-year PFS and OS rates of 69% and 86%, respectively. Patient selection was probably biased and patients with poor general condition or severe comorbidities were certainly not included. However, these results show that in the elderly there is probably a subgroup of fit patients who may benefit from intermediate-dose melphalan plus ASCT in combination with novel agents. Obviously the role of this approach remains undetermined in the era of novel therapies and it should not be proposed out of a clinical trial.

The Role of Maintenance/Consolidation

Maintenance. If one of the objectives of MM treatment is to maintain remission, some form of maintenance therapy is needed. Following positive results with thalidomide maintenance in the context of HDT/SCT, lenalidomide appears to be an excellent candidate for a maintenance strategy because of a better tolerance. Three randomized trials, 2 in the HDT/ASCT paradigm^{128,129} and 1 in elderly patients,¹⁵⁴ have been reported. In all three studies lenalidomide was prescribed at low doses (10-15 mg/day) and was prescribed until progression. In all three studies there was a dramatic superiority in the lenalidomide arms as compared with control arms in terms of PFS or TTP. But until now there is no significant difference as regards OS. Therefore it is too early to recommend this strategy to all patients. Longer follow-up is needed, especially because relapses occurring during lenalidomide maintenance might be more difficult to treat, and OS after salvage might be shorter in the lenalidomide arms. This raises the question of the optimal duration of maintenance therapy and there are 2 possibilities: (1) until progression, which might be the best choice if OS is superior in the lenalidomide arms of these three studies; (2) fixed duration in order to limit the risk of resistance to lenalidomide.

Consolidation. The role of long-term maintenance treatment is to control the residual clone, and IMiDs might be useful in this setting partly because of their immunologic affects. However, there is another way to prolong remission, which is to further increase the CR rate or to upgrade the level of remission by a consolidation treatment with a short and intensive treatment. This approach has been mostly used in the HDT/ASCT setting. Some investigators stated that post-ASCT thalidomide was acting primarily as a consolidation by increasing CR/VGPR rate, because only patients who were not in CR/VGPR after ASCT did benefit from thalidomide treatment.^{121,125} Recent studies have shown that consolidation with lenalidomide or bortezomib did increase the CR or CR plus VGPR rates as well.^{187,188} If consolidation is needed, a combination might be more active than a single drug. The Italian group has shown that post-ASCT consolidation with

a combination of bortezomib, thalidomide, and dexamethasone (VTD) may upgrade the level of remission and yield molecular remissions.¹⁸⁹ However, again this apparent benefit is at the expense of an incidence of peripheral neuropathy which is as high as 14%. The respective role of consolidation and maintenance in PFS prolongation is still unknown and studies are ongoing to address this question. One important aspect to consider will be the efficacy/toxicity ratio.

Newer Therapeutic Agents

With up-front use of novel agents, CR and PFS rates are improving dramatically and one can hope that some patients will be cured, which was so rarely the case with HDT/ASCT alone. Prognosis of patients with poor-risk characteristics has improved but we know that the majority of patients will still experience relapse. Moreover, some subgroups of patients including patients with primary plasma cell leukemia or with del(17p) still represent an unmet medical need because we have currently no satisfactory treatment. Finally, treatment of relapses occurring under maintenance treatment will probably constitute a new challenge. We therefore certainly need new agents for the near future to further improve OS in MM.

Currently the most interesting agents are new IMiDs and new proteasome inhibitors. Pomalidomide is a promising new IMiD that is actually the third to enter the clinic. It is more potent *in vitro* than thalidomide and lenalidomide. Phase I was performed some years ago and showed that oral administration of this agent was well tolerated in daily doses ranging from 1 to 5 mg.¹⁹⁰ The most frequent adverse event was myelosuppression. The first phase II study on 60 patients with relapsed or refractory MM was published only recently.¹⁹¹ At a dose of 2 mg/day in combination with low-dose dexamethasone, the response rate was 63% including 33% CR plus VGPR. Interestingly, the response rate was 40% in patients refractory to lenalidomide and 74% in patients with high-risk cytogenetic or molecular markers. Again, the most frequent adverse event was myelosuppression with 35% grade 3-4 neutropenia. Further studies are ongoing to determine the best dose and schedule of administration as well as the efficacy in patients who fail to respond to other novel agents.¹⁹²

Carfilzomib is the first of new proteasome inhibitors that are currently under development. It is a highly selective and irreversible proteasome inhibitor and is administered intravenously. The most important finding of the phase I study was the absence of grade 3-4 peripheral neuropathy.¹⁹³ In following studies, carfilzomib has been administered on 2 consecutive days every week for 3 weeks, in 28-day cycles, at a dose of 20 and 27 mg/m². Preliminary results show a response rate of approximately 50% in bortezomib-naïve patients and 18% in bortezomib-pretreated patients.¹⁹⁴ Treatment-emergent peripheral neuropathy is uncommon, which appears to be an important difference with bortezomib.

A large number of other agents targeting surface receptors or signal transduction pathways are currently being tested.^{47,195} Although they are not very effective as single agents, some of them look attractive, as their combination with bortezomib or lenalidomide might be synergistic. Among them, the most promising are the Akt-inhibitor perifosine,¹⁹⁶ the anti-CS1 antibody elotuzumab,¹⁹⁷ and the histone deacetylase inhibitors vorinostat¹⁹⁸ and panobinostat.¹⁹⁹

Conclusion

In the year 2000, only 2 classes of anticancer drugs were active in MM: alkylating agents including high-dose melphalan, and corticosteroids including high-dose dexamethasone. In 2010, we now have 4 classes of active agents with the addition of IMiDs (thalidomide, lenalidomide, and in the near future pomalidomide) and of proteasome inhibitors (bortezomib and, in the near future, carfilzomib and others).

The introduction of the 3 new agents induced a number of major improvements in the prognosis and of significant changes in MM management: (1) improvement of OS after relapse; (2) CR rate increased both in younger patients eligible for HDT/ASCT and in elderly patients; (3) increased duration of first response, because of either upgrading of the response level or controlling the clone by prolonged treatment; (4) improvement of response rate and PFS in some subgroups of patients with poor-prognosis characteristics; and (5) as a consequence of all of these aspects, dramatic improvement of PFS and OS in younger patients as well as, at last, in older patients.

There are obviously many questions to address in the next few years but maybe the most important are in relation to the general strategy of MM treatment: (1) Is an aggressive approach with HDT/ASCT still necessary or at least in which patients? (2) Should we use all active agents up-front with the objective of curing at least some patients, with the risk of selecting resistant clones, or should we use a more gentle approach with a sequential use of the four classes of active agents? (3) Prolonged treatment is certainly useful to upgrade the response level and prolong remission duration, but what are the risks of very long treatments and what is the optimal duration of maintenance?

This 10-year period has been thrilling with a large number of exciting advances. However, it is fair to say that these new agents and new diagnostic procedures are very expensive and that optimal treatment is not possible in all countries because of financial and administrative restrictions.

Disclosures

The author has no relevant relationships to disclose.

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