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Management of multiple myeloma and related-disorders: guidelines from the Italian Society of Hematology (SIE), Italian Society of Experimental Hematology (SIES) and Italian Group for Bone Marrow Transplantation (GITMO)

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A B S T R A C T

Objectives. Perceiving the need for rigorous recommendations to facilitate decisions concerning the management of patients with multiple myeloma (MM), the Italian Society of Hematology (SIE) and the two affiliate societies (SIES and GITMO) commissioned a project to develop guidelines for the therapy of MM using evidence-based knowledge and consensus formation techniques.

Methods. After a comprehensive systematic review of 1,450 papers, an Expert Panel formulated and graded sixty recommendations according to the supporting evidence. Evidence gaps were filled with twenty-two consensus-based statements. High grade recommendations (grade A) are reported below.

Results. Treatment should be immediately initiated in MM patients with related organ damage: those patients aged below 65 years who do not have severe co-morbidities should receive autologous stem cell transplantation, while patients not candidates for autologous stem cell transplantation should receive oral melphalan and prednisone. Interferon-α should not be associated with conventional chemotherapy, but it can be offered with or without steroids as a maintenance therapy to patients who have reached a plateau phase. High-dose dexamethasone-containing regimens or high-dose dexamethasone alone are recommended as a first-line therapy when cytoreduction is urgently required (i.e., MM with spinal cord compression or with rapidly progressive renal failure). MM patients with moderate-to-severe anemia should receive erythropoietin, while patients with bone disease or osteopenia should receive long-term bisphophonates. Recommendations for the management of the clinical manifestations caused by the monoclonal protein (i.e. hyperviscosity, cast nephropathy, AL amyloidosis) and of solitary bone and extramedullary plasmacytoma were also elaborated.

Conclusions. A substantial proportion of clinical care for MM can be guided by evidence-based treatment recommendations.

Key words: multiple myeloma, clinical practice guidelines, systematic review, stem cell transplantation, evidence-based knowledge.

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Multiple myeloma (MM) accounts for 10% of all hematologic malignancies[1] and is characterized by a poor prognosis, the median overall survival (OS) of patients receiving conventional chemotherapy being only 36-40 months at the best institutions.[2-3] Infections and renal failure are the major life-threatening complications, while anemia and bone disease are the principal causes of the poor quality of life of MM patients.[4] Attempts to improve upon the dismal clinical outlook of patients with MM and to ameliorate their quality of life have been made in recent years by investigating innovative antitumor strategies and searching for new interventions for bone, renal and infectious complications.

Currently, physicians are facing the difficult task of innovating their therapeutic conduct according to the newly proposed strategies. Subjective integration of older and newer pieces of evidence may lead to conflicting conclusions and large variations in clinical practice. Evidence-based treatment recommendations may help physicians to offer patients the best available treatments. Consensus-based statements can be used when evidence gaps occur in some relevant clinical areas.

In 2001, the Italian Society of Hematology (SIE) began an initiative to sponsor evidence-and-consensus-based guidelines in the therapy of selected diseases. In 2002 the Italian Society of Experimental Hematology (SIES) and the Italian Group for Bone Marrow Transplantation (GITMO) shared this aim with SIE and decided to focus their efforts on the therapy of MM and related disorders. The guidelines elaborated during this project are presented here.

Design and Methods

Organization

The SIE charged two chairmen (ST and GB) with the development of the present guidelines: they invited an Expert Panel (EP) of 7 senior hematologists, selected for their expertise in research and clinical practice of MM. An Advisory Council (GB and MM) was also convened to support the systematic review of literature and the consensus phase.

Literature inquiry

The Advisory Council searched the following evidence bases: PubMed, CancerLit, the Cochrane Library, and EMBASE. The first search was performed on 20th July 2002, however, relevant papers published up to 31st May 2003 were subsequently searched. The basic search strategy adopted was: "*Myeloma/therapy**" in MESH. The major hematology, oncology and general medicine journals (Blood, Journal of Clinical Oncology, British Journal of Haematology, Bone Marrow Transplantation, Haematologica, New England Journal of Medicine) were manually searched for relevant papers published from 1992 to 2002. Additionally, the proceedings of the latest annual meetings were searched for relevant unpublished evidence: American Society of Hematology (1995-2002), Italian Society of Hematology (2002), European Haematology Association (2002). The full reference list of the comprehensive systematic review of 1,450 papers (including the abstracts of full papers) is available on request from *marchettim@smatteo.pv.it*.

Definitions

During the first consensus conference, the EP agreed on the following definitions to be used in the present guidelines:[5,6]

Asymptomatic myeloma: bone marrow B-cell-derived clonal disease that is diagnosed through the demonstration of a monoclonal component (MC) in serum ≥ 30 g/L and/or bone marrow plasma cells ≥ 10%; no symptoms or disease-related organ damage or tissue impairment .

Symptomatic multiple myeloma: bone marrow B-cell-derived clonal disease that is diagnosed through the demonstration of MC in serum and/or urine; bone marrow plasma cells ≥ 10%; disease-related organ damage or tissue impairment, including bone lesions.

Non-secretory myeloma: bone marrow B-cell-derived clonal disease that is diagnosed through the demonstration of bone marrow plasma cells ≥ 10%, disease-related organ damage or tissue impairment, including bone lesions; no MC in serum and/or urine or assessed by immunofixation.[6]

Disease-related organ damage: bone lesions (lytic lesions or osteoporosis with compression fractures), anemia (hemoglobin 2 g/dL below the lower limit of normal or hemoglobin <10 g/dL), renal insufficiency (creatinine >173 mM/L), symptomatic hyperviscosity, recurrent bacterial infections (> 2 episodes in 12 months), amyloidosis, hypercalcemia (serum calcium >0.25 mM/L above the upper limit of normal, or > 2.75 mM/L).[6]

Solitary plasmacytoma of bone: B-cell-derived malignancy that is diagnosed through the demonstration of a single area of bone destruction due to clonal plasma cells; bone marrow not consistent with MM; normal skeletal survey (and magnetic resonance imaging [MRI] of spine and pelvis if done); no MC in serum and/or urine (a small MC may sometimes be present); no disease-related organ or tissue impairment.[6]

Extramedullary plasmacytoma: B-cell-derived malignancy that is diagnosed through the demonstration of extramedullary tumor of clonal plasma cells; normal bone marrow; normal skeletal survey;no MC in serum and/or urine (a small MC may sometimes be present); no disease-related organ or tissue impairment.[6]

Disease plateau: stable MC values (within 25% above or below the value at the time response was assessed) maintained for at least 3 months.[5]

Refractory disease: minimal decrease or increase (<25%) in the concentration of serum or urinary MC and/or an increase in the size of existing bone lesions and/or development of new bone lesions, soft tissue plasmacytomas or hypercalcemia not attributable to any other cause.

Relapse from complete remission: reappearance of serum or urinary MC on immunofixation or routine electrophoresis, confirmed by at least one further investigation and excluding oligoclonal immune reconstitution and/or >5% plasma cells in a bone marrow aspirate or on trephine bone biopsy; development of new lytic bone lesions or soft tissue plasmacytomas or definite increase in the size of residual bone lesions (development of a compression fracture does not exclude continued response and may not indicate progression) and/or development of hypercalcemia (corrected serum calcium > 11.5 mg/dL or 2.75 mM/L) not attribuable to any other cause.[5]

Evidence analysis

During the first consensus conference, the EP also agreed on the major areas of concern in the therapy of MM, thus identifying the therapeutic issues for the guidelines. Each member of the EP, along with a member of the AC, was assigned to one or more therapeutic issues. The member of the AC reviewed and selected the available evidence and graded its quality. The grading system chosen for the present project is the one elaborated by the Scottish Intercollegiate Guideline Network.[7] This system primarily classifies evidence according to the study design, thus assigns randomized trials to lev-

el 1, cohort and case-control studies to level 2, and case reports to level 3. Studies belonging to levels 1 and 2 can be further classified into three levels, namely ++, + and -, according to the study and reporting quality. We assigned phase II studies to evidence level 2. Relevant studies (i.e. reports of randomized clinical trials) reported in abstract form only could not be assigned a quality level, but were uniquely classified according to their study design. In the comment to each recommendation, the authors stated whether abstract-based evidence played a relevant role in supporting a specific statement. Evidence deriving from studies not enrolling patients with MM was defined *translated*, according to the SIGN system and assigned a one-step lower evidence level than it would have been given according to the study design and quality if it had dealt with MM patients.

Formulation of recommendations

Each member of the EP formulated evidence-based recommendations based on the literature review: he/she also added expertise-based recommendations when relevant areas could not be addressed by the available evidence but indirect evidence could support a statement. Recommendations for therapeutic choices were either positive (suggestion to perform an action), negative (suggestion not to perform an action), indifferent (option to choose among two or more non-superior therapies) or provisional (positive indication to enroll patients into clinical trials testing the index therapy). All the recommendations were graded class A if supported by consistent and applicable level 1 evidence (at least one level 1++ trial or some consistent level 1+ trials), class B if evidence was derived from consistent results of level 2++ studies or was extrapolated from level 1+/1++ trials, class C if supported by grade 2+ studies that could be applied directly to the object population and provided consistent results, or level 1++ studies from different populations (translated evidence), and grade D when supported by poor quality evidence or evidence extrapolated from grade 2+ studies, and thus sustained mainly by the experts' opinion.

A first round of consensus for the proposed recommendations was obtained through paper questionnaires, according to the Delphi Panel technique. The AC meshed the Panel comments and the full body of recommendations was finally discussed during four Consensus Conferences held in Milan on 4 July 2002, 20 October 2002, 19 December 2002 and 25 January 2003.

Results

Frontline therapy: indications to start treatment

Patients with symptomatic MM should be treated immediately. In contrast, for patients with asymptomatic MM, immediate chemotherapy does not offer any survival benefit over that provided by delayed chemotherapy, as convincingly demonstrated by several controlled studies[8,9] and confirmed by a recent meta-analysis pooling the results of these trials.[10] Thus, patients with MM but no related organ damage must be followed up closely and should start treatment when signs of disease progression develop. The time to disease progression for these patients is reported to vary from less than 1 year to approximately 3 years, and may be predicted by several factors.[11-13] Skeletal-related events (i.e. pathologic fractures, hypercalcemia) were reported to occur in a certain fraction of patients at the time of progression into symptomatic MM.[13] MRI of the spine may help in assessing impending bone complications.[14]

Ongoing studies are evaluating bisphosphonates and/or thalidomide as initial therapy for patients with asymptomatic MM. However, only preliminary data on the efficacy of these drugs on progression into symptomatic disease are available.[15] Therefore, evidence in this setting was judged by the Expert Panel not sufficient to recommend the routine use of these drugs in clinical practice, outside approved clinical trials.

Recommendations

Treatment must be started immediately in patients with MM and related organ damage (anemia, hypercalcemia, bone lesions, renal failure, hyperviscosity, amyloidosis, recurrent bacterial infections) (grade A).

Organ damage should be assessed through the following evaluations: full blood count, serum calcium, serum creatinine, urinary protein, total body X-ray survey, MRI of the spine, periumbilical fat fine-needle biopsy (aimed to assess amyloid fibrils in patients with clinical or laboratory features that suggest the presence of amyloidosis), fundus oculi (aimed to assess the presence of hyperviscosity-related lesions in patients with MC > 40 g/L) (grade D).

Patients with untreated MM should be carefully monitored by physical examination, full blood count, measurement of both serum and urinary MC, serum calcium, serum creatinine, skeletal X-ray (of the spine, pelvis, femur, humerus), and MRI of the spine in patients with MC>30 g/L or IgA MC or Bence Jones (BJ) proteins > 50 mg/day (grade D)

Monitoring of all the above cited aspects, except skeletal imaging, should be repeated at 3 monthly intervals in the first year of follow-up and every 6 months afterwards, if the disease remains in a steady state. Skeletal evaluations can be performed only once a year (grade D).

Autologous stem cell transplantation

Studies on autologous stem cell transplantation (SCT) as a means to overcome chemoresistance in MM patients in whom conventional therapy failed were pio-

neered in the mid 1980s.[16-18] Once the feasibility and efficacy of this procedure had been demonstrated in advanced and refractory disease, autologous SCT was subsequently performed also as primary therapy for patients with newly diagnosed disease. Over the last decade, the interest in this treatment modality has progressively grown and many thousands of patients have so far received autografts worldwide. Autologous SCT for MM currently accounts for more than 25% of all autografts performed in Europe (with the European Bone Marrow Transplant registry having accrued 8362 patients reported from 1986 to 2000)[19,20] and is the second most frequent indication for autologous SCT in the United States.[21] Two prospective, randomized trials[22,23] and one population-based study[24] comparing conventional chemotherapy with a single autologous SCT as first-line treatment for patients aged less than 60-65 years demonstrated the significant benefit from autologous SCT in terms of an increased complete remission (CR) rate, up to 20-40%, and extended event-free survival (EFS) and OS (by 12 to 15 months). However, no plateau in EFS curves could be discerned, suggesting that a single autologous SCT was not curative.

Based on these findings, attempts were made by several groups to improve the results by administering two sequential courses of high-dose therapy and double (or tandem) autologous SCT. Results of a phase II pilot study showed that repeated administrations of melphalan at 200 mg/m^2 could be given safely, with a cumulative mortality rate below 3%, and significantly prolonged the survival in a pair-mate comparison with conventional chemotherapy.[25] Following this study,[5] prospective, randomized trials were started in Europe aimed at exploring the value of double autologous SCT in comparison with a single transplantation as primary therapy for MM patients under the age of 60-65 years. Results of these studies were recently updated[26-30] and are summarized in Table 1. Briefly, two studies showed a significant improvement and prolongation in EFS (from 10% to 20% at 7 years and from a median value of 25 months to 34 months, respectively) with double autologous SCT,[26,29] a finding confirmed also by a trial of double intensive, non-myeloablative therapy and subsequent autologous SCT.[28] Importantly, the 7-year projected OS for patients assigned to double autologous SCT was double that observed in the single transplant arm (42% versus 21%, respectively).[26] In contrast, two other studies failed to demonstrate any difference in EFS and OS between single and double autologous SCT.[27,30] The divergence of survival curves after 4 to 5 years from the start of treatment observed in the French study should raise some caution against any premature conclusion concerning the role of double autologous SCT in studies without a sufficiently long follow-up period.

Transplant-related mortality (TRM) in younger patients with normal renal function who receive high-dose therapy with PBSC support is generally below 5%. However, the risk increases up to 10% or more if the transplant is performed in older patients or in patients with renal failure. The impact of age on outcome of SCT was analyzed in two studies.[31,32] In one study, no statistically significant difference was found in terms of OS and EFS between patients older than 65 years and younger pair-mates treated with full dose melphalan (200 mg/m^2) and double autologous SCT.[31] In the other study, the rate of mortality related to double autologous SCT in patients older than 70 years was 16%, a value lowered to 2% following a reduction in the dose of melphalan to 140 mg/m^2.[32]

In a pair-mate comparison of intensified therapy with PBSC support versus conventional chemotherapy for patients over 60 years of age, the intensified therapy was reported to be of benefit in terms of increased CR rate and extended OS.[32] Taken together, these studies showed that older patients, at least up to 70 years of age, can be considered for autologous SCT (provided their performance status and organ function are satisfactory) and may eventually benefit from this procedure. However, the degree of benefit from autologous SCT in comparison with that from conventional treatment cannot be quantified until prospective randomized trials specifically address this issue. The mortality rate in patients with MM and impaired renal function treated with full dose melphalan (200 mg/m^2) and single or double autologous SCT was reported to be 7% and 13%, respectively.[33,34] No significant improvement in EFS and OS was demonstrated for patients who received double autologous SCT in comparison with patients who were treated with a single course of high-dose therapy.

Decreasing the dose of melphalan from 200 mg/m^2 to 140 mg/m^2 was associated with reduced mucositis and lower TRM, and, more importantly, did not adversely affect the outcome of SCT.[33] A retrospective comparison between patients with renal failure and pair-matched controls with normal renal function failed to demonstrate any difference between the two groups in terms of 3-year projected OS.[35] Thus, it can be concluded that the presence of renal failure should no longer be considered a contraindication to autologous SCT in MM.[36,37] The optimal dose of melphalan for these patients is 140 mg/m^2.

The issue of the best source of hematopoietic stem cells (i.e. bone marrow versus peripheral blood stem cells) was addressed in a prospective randomized study.[38] A trend towards improved survival with PBSC transplantation was observed, suggesting that peripheral blood may be the recommended source of stem cells also in MM patients. In order to collect a sufficient number of stem cells (i.e. CD 34$^+$ cells), chemotherapeutic

Table 1. Comparative studies of autologous SCT in multiple myeloma.

Reference	*Study*	*Country*	*Randomized*	*N. of patients*	*Age (years)*	*Regimens*	*Median follow-up (months)*	*CR (%)*	*EFS (median, months)*	*OS (median, months)*
Standard chemotherapy versus single autologous SCT										
Attal[22]	IFM	France	Yes	100	58	VMCP/BVAP×18 versus	108	14	18	44
				100	57	VMCP/BVAP×4-6→Ctx + MEL 140 + TBI 8Gy		38 (p<0.001)	28 (p<0.01)	57 (p<0.03)
Child[23]	MRC VII	UK	Yes	200	56	ABCM×4-12 versus	42	8	20	42
				201	55	CVAMP×3→Ctx + MEL 200		44 (p<0.001)	32 (p<0.001)	54 (p<0.04)
Blade[21]	PETHEMA	Spain	Yes*	83	56	ABCM/VBAD×12	66	11	34	67
				81	56	ABCM/VBAD×4→MEL 200		30 (p<0.002)	43	65
Single versus tandem autologous SCT										
Attal[26]	IFM94	France	Yes	199	52	VAD×3-4→G-CSF→MEL140	75	42	25	48
				200	52	+ TBI 8Gy versus MEL140; MEL140 + TBI 8Gy		50 (p<0.1)	30 (p<0.03)	58 (p<0.01)
Cavo[29]	BOLOGNA 96	Italy	Yes	110	53	VAD×4→CTX→MEL 200	38	21	25	56
				110	53	versus MEL 200; MEL 120 + Busulfan		24	34 (p<0.05)	60
Fermand[27]	MAG 95	France	Yes	97	50	DEX×2→CTX→VAD×3-4	53	39	31	49
				96	50	→MEL140+ VP16 + CTX + TBI 12Gy versus MEL 140; Mel 140 + VP16 + TBI 12Gy		37	33	73 (p=0.14)
Sonneveld[28]	HOVON	Germany	Yes°	129	55	VAD×3-4X→CTX→MEL70×2	40	14	4yr:15%	4yr:15%
				132	56	VAD×3-4X→CTX→MEL70×2 →CTX + TBI 8Gy		28 (p<0.004)	versus 29% (p<0.03)	versus 33% (p<0.3)
Standard chemotherapy versus tandem autologous SCT										
Barlogie[25]	SWOG, TTI	US	No	152	52	VMCB(P)/VBAP(P)/VAD	114	NA	16	43
				152	52	VAD×2-3→CTX→EDAP →MEL200×2 (<PR, MEL140+TBI 8.5Gy)		41	37 (p<0.0001)	79 (p<0.0001)

**Responders to induction; °after VAD.*

agents that are toxic to bone marrow stem cells (primarily, melphalan and nitrosoureas) and large volume radiation therapy to marrow-containing bones should be strictly avoided. Older age does not impair stem cell harvesting and cannot be considered an exclusion criterion.[39]

Available data to support the choice of the best mobilization therapy are limited; only 3 randomized clinical trials have addressed this issue and 2 of them had a limited sample size.[40-42] Results showed the superiority of combined stem cell factor, filgrastim and cyclophosphamide over cyclophosphamide plus filgrastim,[40] as well as of combined cyclophosphamide and filgrastim over either filgrastim alone[41] or cyclophosphamide alone.[42] Cyclophosphamide, at the dose of 3-4 g/m^2, and G-CSF is one of the most commonly used regimens in clinical practice. The issue of the best conditioning regimen to be administered before autologous SCT was addressed in a randomized, multicenter clinical trial comparing melphalan at a dose of 200 mg/m^2 with combined total body irradiation (TBI) (8 Gy) plus melphalan at a dose of 140 mg/m^2.[43] Melphalan at 200 mg/m^2 was associated with a significantly better 4-year probability of OS, as well as with decreased toxicity and a shorter duration of hospitalization. Full dose melphalan is thus considered the *gold standard* treatment to be used before autologous SCT for MM.

The feasibility and efficacy of purging methods aimed at providing a tumor-free source of repopulating hematopoietic stem cells were investigated in several phase II studies and one large, randomized multicenter clinical trial.[44] Although a marked reduction, by approximately 3 logs, in the number of myeloma cells contaminating the graft was frequently reported,[45] purged autologous SCT did not improve the OS over that produced by unpurged SCT.[45,46] Purging methods are expen-

sive and may delay immunological reconstitution, thereby increasing the risk of infections following autologous SCT.[47,48]

Attempts to prolong the duration of disease control, and possibly the OS, following autologous SCT were made by using IFN-α as maintenance treatment and by giving consolidation chemotherapy before maintenance treatment. A single study that prospectively compared IFN-α versus no therapy reported a significant benefit from the IFN-α in terms of prolonged progression-free survival (PFS) and OS at a median follow-up of 52 months; however, the gain was lost after 77 months.[49] Two additional non-randomized studies, possibly influenced by selection bias, further supported the beneficial role of IFN-α in extending the duration of OS and PFS after autologous SCT.[50,51] Data concerning the role of post-SCT consolidation chemotherapy are currently too limited[52] to draw definitive conclusions.

Multivariate analyses aimed at identifing the risk factors affecting transplant outcome showed the strong and independent prognostic relevance of several variables, including β-2 microglobulin, C-reactive protein, lactic dehydrogenase and creatinine levels.[21,23,25,53,54] Chemosensitive disease before autologous SCT was also associated with a good prognosis.[53] However, refractoriness to conventional therapy does not preclude a favorable outcome with autologous SCT,[55] particularly if high-dose therapy is administered within 1 year of diagnosis.[56] Cytogenetic abnormalities, as identified by conventional karyotype and/or FISH analysis, provide additional important prognostic information. In particular, chromosome 13 monosomy and/or deletions portend a poor prognosis and identify a subset of patients who will not benefit from double autologous SCT,[53,54,57,58] whereas the t(11;14) correlates with a favorable outcome of SCT.[59,60] Finally, there is a consensus concerning the value of post-transplant attainment of CR as a surrogate marker of extended OS and EFS,[21,61] independently of the treatment program (namely, either single or double autologous SCT) by which this important goal is achieved.

Recommendations

Patients with MM who are younger than 65 years should receive high-dose chemotherapy and a single autologous stem cell transplant (SCT), provided that they are free of severe co-morbid conditions (grade A). Double autologous SCT should be performed in those patients who fail to achieve complete remission (CR) after the first SCT (grade B).

Older age (more than 65 years) and renal failure are not per se exclusion criteria for SCT (grade B). Thus, patients aged 65-70 years can undergo SCT, provided that they are free of severe co-morbid conditions and are enrolled into approved clinical trials (grade B).

Peripheral blood is the preferred source of autologous stem cells for the transplant (grade B).

The minimum number of $CD34^+$ cells that needs to be harvested in order to assure prompt hematopoietic recovery following high-dose therapy is 2×10^6 /Kg per each planned transplantation (grade B). The use of melphalan before stem cell collection should be avoided (grade B) and radiotherapy must be limited to highly selected patients (grade B).

There is not enough evidence to recommend one mobilization regimen with respect to another: the most commonly employed regimen includes cyclophosphamide and G-CSF (grade B).

Purging of harvested cells is not recommended because it has no beneficial impact on the duration of survival (both OS and EFS) and can be detrimental since it may be associated with an increased risk of infections (grade A).

High-dose melphalan (200 mg/m^2) is the gold standard treatment for patients below 65 years and/or with normal renal function (grade A). Dose-reduction (140-100 mg/m^2) should be considered in order to decrease the toxicity in patients older than 65 years and in patients with renal impairment.

There is insufficient evidence to recommend consolidation chemotherapy after autologous SCT (grade B).

IFN-α (alone or associated with steroids) is not recommended as routine maintenance therapy after autologous SCT, but it can be considered within approved clinical trials (grade B).

Data are insufficient to recommend the use of steroids or thalidomide as maintenance therapy after autologous SCT, thus these therapies should be used only within approved clinical trials.

Allogeneic SCT

More than 2000 MM patients have received allogeneic SCT worldwide and the annual rate in Europe is about 300 procedures/year.[19] Although the mortality related to transplantation has recently significantly decreased in comparison with the past TRM,[62] fatal complications – most frequently, infections – still occur in 25% to 30% of patients, a value much higher than that expected with autologous SCT. It should be noted that TRM is twice as high in patients with graft-versus-host disease (GVHD),[63] while the lowest TRM (8%) is encountered for syngeneic grafts.[64] A low TRM is also reported in upfront transplants.[65] Contrariwise, TRM is high in patients over 50 years of age,[66] in recipients of grafts from unrelated donors,[67] and in those with advanced refractory or progressive disease.[65]

In comparison with autologous SCT, patients surviving allogeneic SCT attain more frequent and more durable molecular remissions, as a result of the well recognized graft-versus-myeloma effect.[63,68-83] Overall

survival at 3 years after an allogeneic SCT is 56%, and declines quite slowly thereafter.[62] Unfortunately, no plateau has been observed in the survival curves.[62]

Different conditioning regimens can be employed for allogeneic SCT: TBI-based conditioning regimens and busulfan-cyclophosphamide regimens produced similar TRM, CR and CR durations.[84-88] The outcomes of non-myeloablative allogeneic SCT have been assessed in 22 case series enrolling overall 270 patients, mainly with refractory/relapsed disease.[89-91] A lower TRM was reported with the non-myeloablative regimens compared with myeloablative conditioning regimens, but the long-term benefit is currently unknown.[90] Non-myeloablative allogeneic SCT has also been employed as consolidation after autologous SCT, along with donor lymphocyte infusion (DLI),[92,93] but this is still an experimental intervention.

Recommendations

Current data do not support the standard use of allogeneic SCT from matched related donors as primary therapy for MM (grade B). Myeloablative allogeneic SCT from a sibling donor may be considered frontline treatment for patients aged <50 years who are not expected to benefit from autologous SCT, for example are patients with chromosome 13 deletion. However this procedure should be performed in the context of approved clinical trials.

If a twin donor is available, syngeneic SCT should be offered frontline up to 65 years of age (grade B). Unrelated donor SCT is not currently recommended and must therefore be performed only in the context of approved clinical trials (grade D).

Allogeneic SCT should favor the use of peripheral stem cells (grade B from translated level 1+ evidence). Evidence does not support a clear-cut advantage of TBI-based preparative regimens, thus the choice depends upon the center's policy, the availability of TBI and the patient's prior exposure to radiation (grade B). The use of reduced-intensity or non-myeloablative conditioning regimens is still experimental and should be performed in the context of approved clinical trials. There is no evidence to recommend alternative regimens to cyclosporine and methotrexate for GVHD prophylaxis since this combination remains the standard immunosuppressive regimen in myeloablative allogeneic SCT (grade B). Maintenance therapy is not recommended in recipients of an allogeneic SCT.

Standard chemotherapy

The first evidence that chemotherapy improved the prognosis of MM patients in comparison with placebo dates back to the late 1960s.[94] Melphalan, first introduced in 1958, and subsequently supplemented with prednisone (MP),[95] has been the highway of conventional therapy for several decades, although the response rate is only in the 50-60% range and the median OS does not exceed 3 years.[96,97] Melphalan is easy to use on an out-patient basis and has a low profile toxicity; however, it should be used with caution in patients with renal failure,[98] and should be avoided in patients who are candidates for a subsequent autologous SCT.[99,100]

Combined chemotherapy regimens, including or not melphalan, have been widely explored in an attempt to improve the prognosis of MM patients. Two recent meta-analyses considering 3,814 and 6,633 patients demonstrated that combined chemotherapy failed to significantly extend the OS in comparison with that achieved by MP, at the expense of increased toxicity and worse tolerance.[96,97] Regimens including melphalan and/or nitrosourea are toxic to hematopoietic stem cells and should be avoided if stem cell harvesting is planned. Vincristine and doxorubicin, given by 4-day continuous infusion, along with pulsed dexamethasone (VAD) was initially used as salvage therapy for patients in whom prior alkylating agent therapy failed,[101] and subsequently as primary induction of remission for previously untreated patients.[102,103] In comparison with MP, the VAD regimen has several advantages, including that it produces a more rapid response, dose reductions are not needed in the case of impaired renal function and, more importantly, it does not cause stem cell injury.[104,105] Due to these properties, VAD has become the most popular treatment used in clinical practice in an attempt to reduce tumor cell mass before autologous SCT. However, in more recent years the popularity of VAD has been tempered by its major disadvantages, which include the inconvenience and economic costs of a 4-day continuous infusion, the risk of cathether-related infections and thrombosis, as well as its toxicity (alopecia, cardiac toxicity, neurotoxicity). Some of the major toxicities of VAD may be overcome, or at least reduced, by administering pulses of high-dose dexamethasone. Although no controlled clinical trial has so far been conducted in an attempt to evaluate the role of this regimen in comparison with VAD as primary induction of remission, both the rate and rapidity of response reported in a phase II study with dexamethasone alone[106] make this a suitable therapy also for patients with newly diagnosed MM, particularly those with severe pancytopenia and/or impaired renal function.

After the role of thalidomide in the management of patients with advanced and refractory MM had been established,[107] many phase II and phase III studies were designed in an attempt to evaluate the efficacy and toxicity of combined thalidomide-dexamethasone as first-line therapy for patients with newly diagnosed disease. Preliminary results of 3 phase II studies so far reported were promising and suggested that this regi-

men may provide a valid alternative to VAD or high-dose dexamethasone for induction of remission in younger MM patients who are candidates to receive autologous SCT.[108-110] However, evidence is not sufficient to recommend the use of thalidomide and dexamethasone in routine clinical practice, outside the context of approved clinical trials. IFN-α was added to cytotoxic drugs as front-line induction of remission in an attempt to improve the results obtained with chemotherapy alone. Two meta-analyses of both individual patient data and published data showed marginal, albeit significant, benefits from combined chemotherapy and IFN-α in comparison with chemotherapy alone. The benefits were seen in increased response rate and extended PFS (by 5-6 months), but not in OS.[111,112] Moreover, in the IFN-treated patients the quality of life was significantly reduced during the first year of therapy.[113]

The role of IFN-α as maintenance therapy following remission induction chemotherapy[114] was also investigated. A small, but significant, prolongation of PFS, by 4-7 months, and OS, by approximately 7 months, was reported for IFN-α in two meta-analyses of published studies.[111,112] A third meta-analysis evaluated the long-term survival of patients treated with IFN-α; no significant benefit in *mean lifetime survival* was demonstrated in these patients.[115]

Therapeutic advantages offered by IFN-α must be balanced against the toxicity and side-effects reported by most of the patients. Side effects may be mild in a certain fraction of patients, and eventually resolve after the first weeks of treatment. However, in approximately 20-30% of cases treatment discontinuation is required due to relevant side effects.[111,112] Toxicity may reduce the quality-adjusted survival advantage to clinically non-relevant values.[113] Finally, it can be predicted that approximately 50% of patients will refuse IFN-α therapy if side effects and potential clinical benefits of IFN-α are clearly illustrated in advance.[116]

In a randomized clinical trial addition of alternate-day prednisone to IFN-α was reported to be more effective than IFN-α alone.[117] In contrast, there is no proof that monthly courses of high-dose dexamethasone are superior to daily doses of prednisone, whereas alternate-day prednisone at the dose of 50 mg significantly increased the PFS and OS in comparison with alternate-day prednisone at the dose of 10 mg.[118]

Recommendations

Melphalan and prednisone is the treatment of choice for previously untreated patients with symptomatic MM who are not candidates for autologous SCT (grade A).

The most commonly employed regimen is the following: oral melphalan at 0.25 mg/kg/day×4 days and prednisone 2 mg/kg every day for 4 days. The therapy should be repeated every 28 days until a plateau is reached.

Combination chemotherapy offers no clear advantage over melphalan and prednisone in terms of extended survival (grade A).

Dexamethasone-containing regimes (VAD or VAD hybrids) should be preferred for patients who require rapid cytoreduction (i.e. patients with renal failure, hypercalcemia, spinal cord compression, hyperviscosity syndrome) (grade C).

High-dose dexamethasone should be given as initial therapy in patients with renal failure, pending decisions on subsequent chemotherapy and the outcome of full supportive measures, and/or in patients with severe pancytopenia. Subsequent combination chemotherapy in patients with renal failure should be VAD-based (grade C). In patients with renal failure who are not candidates for autologous SCT and for whom adriamycin or dexamethasone are contraindicated, melphalan or cyclophosphamide-based regimens should be dose-reduced; oral melphalan should not be used in patients with a glomerular filtration rate (GFR) below 30 mL/min, unless they are on hemodialysis. The initial melphalan dose should be reduced to 50% if the GFR is below 40 mL/min (grade D). The cyclophosphamide dose should be reduced by 25% if the GFR is below 40 mL/min and by 50% is the GFR is less than 10 mL/min (grade D).

Thalidomide, in combination with dexamethasone or chemotherapy, cannot be recommended as routine first-line therapy and should be used in the context of an approved clinical trial (grade D).

IFN-α should not be associated with first-line conventional chemotherapy given the lack of clinical benefit (grade A). Patients who respond to first-line conventional chemotherapy can be offered IFN-α as maintenance therapy with or without steroids (grade A). Despite the high-level evidence supporting the efficacy of IFN-α, the strength of this recommendation is low because of the modest clinical benefit, weighed against the frequent side effects. Standard treatment with IFN-α is 3 MU sc three times a week. No recommendation can be made regarding the duration of treatment. Data are insufficient to recommend the use of pegylated-IFN instead of standard IFN-α.

Data are insufficient to recommend the use of steroids alone or thalidomide as maintenance therapy after standard chemotherapy, thus these therapies should be used only within approved clinical trials.

Therapy for refractory and relapsed patients

Salvage therapy is offered to a heterogeneous group of patients, including those who are primary refractory to, or progress on first-line therapy, and patients relapsing (either with a resistant or a sensitive disease) after frontline therapy. The clinical difference among these subgroups has been reported.[119,120] Candidates for autologous SCT who are primary refractory to VAD-based

therapy may benefit from subsequent high-dose chemotherapy and autologous SCT.[3,21,55,84,121] Patients who are not candidates for autologous SCT and who are primary refractory to frontline conventional chemotherapy, may primarily benefit from thalidomide and/or further standard chemotherapy.[15,107,122-141]

Relapse or disease progression eventually occurs in most patients who receive autologous SCT, whether single or double, or allogeneic SCT. Provided that sufficient autologous stem cells are available, patients relapsing after a single transplantation may undergo a second autograft, however TRM increases up to 10%.[77,84,142-146] In contrast, a rescue transplant for patients relapsing after prior frontline double autologous SCT was reported to be associated with an OS of 19% at 2 years.[63] In patients progressing or relapsing after allogeneic SCT, donor lymphocyte infusions (DLI) can induce a complete response.[73,147]

Patients relapsing after several lines of treatments have been treated with novel drugs, such as thalidomide, alone or associated with dexamethasone, or proteasome inhibitors.[148,149]

Response rates to thalidomide increase as the cumulative dose of this drug increases,[133,150] but good response rates may also be achieved with doses of 200 mg per day or lower,[151-153] and tolerability is better with a low-dose schedule. Unfortunately, patients with cytogenetic abnormalities have a worse prognosis also with thalidomide treatment.[133] Dexamethasone and eventually added chemotherapy further increase response rates to thalidomide, but also significantly increase the thromboembolic risk, which may reach up to 5% per treatment month.[154-156] Nevertheless, venous thromboembolism did not prove to have a negative impact on patients' survival,[155] and most patients could continue thalidomide and dexamethasone therapy without progression or relapse of venous thromboembolism.[157] Thalidomide frequently induces sensory-motor neurologic defects which may be irreversible.[158,159]

Recommendations

Management of refractory patients

Patients who are not candidates for autologous SCT and are primary refractory to MP should receive thalidomide associated or not with conventional chemotherapy (grade B).

Candidates for autologous SCT who proved primary refractory to VAD are recommended to proceed to autologous SCT (grade A).

Patients who proved refractory to autologous SCT, should not be enrolled into a further autologous SCT and should receive thalidomide associated or not with conventional chemotherapy.

A thalidomide dose of 200 mg/day is effective and well-tolerated (grade B). Combinations of thalidomide with either high-dose dexamethasone or chemotherapy should be preferred. Patients who are treated with thalidomide combined with dexamethasone, and possibly additional chemotherapy, should be monitored for thromboembolic complications and should receive prophylaxis against deep vein thrombosis (grade C). However, evidence is not sufficient to provide recommendations regarding the best prophylaxis of thromboembolism in these patients.

Management of relapsed patients

Patients not eligible for first-line autologous SCT and who have relapsed after first-line MP should receive thalidomide with or without conventional chemotherapy (grade B).

Patients who relapse after autologous SCT should be offered an allogeneic SCT, provided that they are younger than 50 years and have a family donor: the procedure should, however, be performed within approved clinical trials. When relapse occurs after a prolonged remission or there is not a matched sibling donor and autologous stem cells are available (> 2×10^9/Kg), a further autologous SCT is recommended, below the age of 65 years (grade B): over the age of 65, the same procedure may be considered with a dose reduction. Debulking is recommended before both autologous and allogeneic SCT (grade D).

The recommended treatment for patients who relapse after autologous SCT, when neither a matched donor nor autologous stem cells are available, is thalidomide associated with dexamethasone, and possibly added chemotherapy (grade B). DLI should be considered for patients who progress or relapse after allogeneic SCT (grade B).

Myeloma complications

Renal failure

Approximately 20% of patients with multiple myeloma have a creatinine level ≥ 2.0 mg/dL (173 μmol/L) at diagnosis. The two major causes of compromised renal function are urinary light chain excretion and hypercalcemia. Dehydration, infection, non-steroidal anti-inflammatory agents, and roentgenographic contrast media may contribute to acute renal failure.[160,161] The risk of renal failure with roentgenographic contrast media is minimal if dehydration is avoided. In fact, less than 1% of all episodes of acute renal failure in MM patients were temporally related to administration of contrast media.[162] Hyperuricemia may contribute to renal insufficiency but can be treated easily. Amyloid deposition may also contribute to renal failure.

Renal function may recover in more than half of the patients,[161,163-165] usually within the first three months.[163,166] Recovery of renal function has been shown to improve OS in most studies.[165-172]

Maintenance of a high urine output (3 L/day) is important in order to prevent renal failure in patients with Bence Jones proteinuria. Prompt treatment of hypercalcemia and correction of dehydration and electrolyte imbalance are also crucial. Acute renal failure may be reversed by a high fluid intake (> 3 L/24h).[165] Patients randomized in a controlled trial to take alkali fared marginally better than the others, but the difference was not statistically significant.[165] Plasma exchange is effective in removing the monoclonal light chains responsible for renal failure,[173-176] and may restore normal renal function in more than half of patients.[177-179] The efficacy of plasma exchange in preventing the initiation or continuation of dialysis is more evident in patients with rapidly progressive renal failure secondary to MM.[167,175] A small randomized trial[167] and a non-randomized comparative study[179] also reported an improvement in OS in patients treated with plasma exchange: the OS benefit was mainly prolonged in those patients whose renal function recovered.

Recommendations

Renal failure should be prevented in MM patients by avoiding dehydration (grade D) and nephrotoxic drugs (non-steroidal anti-inflammatory agents, nephrotoxic antibiotics), by promptly treating infections and by correcting dehydration, hypercalcemia and hyperuricemia (grade D).

Renal biopsy is not essential in MM patients who have renal failure. Furthermore, the risk of severe peri-procedural bleeding in patients with amyloidosis should be carefully evaluated.

MM patients with renal failure should be rehydrated with intravenous fluids (saline) to achieve a urine flow of over 3 liters per day (grade B). Evidence is not sufficient to recommend urine alkalinization.

Plasma exchange in combination with corticosteroids is recommended in MM patients with rapidly progressing renal failure (grade B).

Dialysis should be offered to patients with end-stage renal disease. Both hemodialysis and peritoneal dialysis are equally effective long-term replacement therapies (grade B). Evidence is not sufficient to recommend renal transplantation in MM patients with end-stage renal failure.

Anemia

Anemia is present in two thirds of patients at diagnosis of MM. Anemia reflects the course of the disease since it worsens during resistant or progressive disease, but it ameliorates when the disease is controlled by treatment. Recombinant human erythropoetin (rHuEpo) has extensively been used throughout the course of the disease to increase Hb concentration, to reduce transfusion requirement, and to improve the quality of life (QoL). A total number of 630 MM patients were randomized in 8 trials examining anemia and erythropoietin use.[180-187] Eligibility criteria most often included hemoglobin values below 10 g/dL.[180-187] The response rate varied from 31% to 78% depending on the criteria for defining response. These values are similar to those observed in the general cancer population.[188] In MM, the response rate was influenced by the disease duration,[187] the ratio between the observed and the predicted serum erythropoetin concentration,[183] and the rHuEpo dose.[183,184] The response rate at 4 weeks was the most powerful predictor of a durable response.[186] Two randomized studies[183,184] reached the conclusion that 5000 UI per day is the optimal dose (e.g, from 30,000 to 40,000 UI per week). This cumulative dosage can safely be given once weekly.[189] Both direct[181] and translated evidence from a miscellanous cancer population indicates that rHuEPO has a definite effect on the QoL which is directly related to the improvement of anemia.[185,188,190-192] So far, no statistically significant benefit on OS has been reported.[186]

Darbepoetin-α has recently been assessed in a double-blind randomized trial that enrolled 344 MM and lymphoma patients[193] and found to be effective on hematologic parameters and QoL.

Recommendations

MM patients with a hemoglobin level below 10 g/dL should receive rHuEPO (grade A).

The initial dose should not be lower than 30,000 UI/week (grade B).

rHuEPO should not be continued in MM patients who have not experienced an increase of hemoglobin concentration of at least 1 g/dL after 4 weeks of treatment (grade D).

Full blood count, reticulocyte count, and iron status (serum ferritin, serum transferrin saturation) should be assessed before starting therapy and monitored during the treatment (grade D).

Bone lesions

Several randomized trials have shown that, compared to placebo, bisphosphonates reduce skeletal-related events (SRE) and bone pain in MM patients. One meta-analysis by the Cochrane Myeloma Group pooled data from 11 randomized trials comparing oral clodronate, intravenous pamidronate or intravenous ibandronate versus placebo.[194] This meta-analysis, including a total of 2,183 assessable patients, showed a pooled reduction of 41% in vertebral fractures and a significant reduction of pain in patients treated with biphosphonates rather than placebo. Subgroup analysis showed that bisphosphonates significantly reduced the occurrence of SRE in early stage MM patients who received pamidronate (level 2)[195] or clodronate (level 1$^+$)[196,197] in

the absence of bone lesions. Another subgroup analysis showed that pamidronate reduced SRE in MM patients who already had skeletal fractures before study entry.[198] Notably, MM patients with advanced disease (on a second or subsequent antimyeloma regimen) who received pamidronate lived longer than MM patients who received placebo.[198] A few randomized studies have been published subsequently to the meta-analysis by Cochrane Myeloma Group.

One study compared intravenous ibandronate versus placebo, but did not show any positive effect on bone morbidity or OS.[199] Two randomized studies were designed as non-inferiority studies and compared intravenous zoledronic acid with intravenous pamidronate.[200,201] These studies also introduced time to first SRE as an additional statistical end-point to minimize the bias of analyses based only on events per person-years.[202] Pamidronate and zoledronic acid showed similar effects on bone mobidity and similar safety profiles. These conclusions have very recently been confirmed in the 25-month final analysis of one of the studies.[200]

The optimal duration of bisphosphonate therapy is not known since most of the trials report follow-ups shorter than 24 months with the exception of the above mentioned recent study[203] in which intravenous pamidronate or zoledronic acid were safely administered every 3-4 weeks for 24 months. However, renal failure and hypocalcemia may occur at any time during therapy with bisphosphonates. Thus, careful monitoring is mandatory, with special attention being given to serum levels of creatinine and calcium, and albuminuria. Any unexplained albuminuria (more than 500 mg/24 hours) or any increase of more than 0.5 mg/dL in serum creatinine or an absolute value of more than 1.4 mg/dL in MM with normal baseline values requires discontinuation of the drugs until the renal problem is resolved.

Bisphosphonates are also employed to treat hypercalcemia in association with hyperhydration. Pamidronate has been shown to be superior to placebo and clodronate,[204,205] while ibandronate has been shown to be superior to placebo.[206] More recently, zoledronic acid has been proven more effective than pamidronate[207] as it produces a higher complete response rate, a longer response duration, and a longer time to relapse.

Recommendations

MM patients with bone disease or severe osteopenia (either newly diagnosed or relapsed or refractory) should receive bisphosphonates (grade A). Long-term therapy (at least 12 months) is recommended (grade D).

According to the preferences of both the physician and the patient, the following treatments may be offered: oral clodronate at 1600 mg/day, intravenous pamidronate 90 mg every 4 weeks, intravenous zoledronate 4 mg every 4 weeks (grade D).

Serum creatinine, urea and total calcium and urinary albumin should be monitored before and during treatment (grade D). Dose reduction should be considered for patients with renal failure who require bisphosphonates for bone disease (grade D).

Any unexplained albuminuria (more than 500 mg/24 hours) or any increase greater than 0.5 mg/dL (44 μmol/L) in serum creatinine or an absolute value of more than 1.4 mg/dL (124 μmol/L) in a MM patient with normal baseline values requires discontinuation of bisphosphonates (grade D).

Treatment of MM-related hypercalcemia should be started at a corrected serum calcium level greater than 3.00 mMol/L (or 12 mg/dL) (grade A).

Patients should be hydrated with saline to maintain diuresis greater than 2.5 L/day and should receive intravenous bisphosphonates (grade B): a single dose of 4 mg zoledronic acid should be infused in 15 minutes and with an infusion volume of 100 mL, in order to limit the frequency of renal complications (grade B). Retreatment with the same drug (zoledronic acid), at higher doses (8 mg), may be considered for patients who relapse or who are refractory to prior therapy (grade B).

Spinal cord compression

The frequency of spinal cord compression at presentation is based on old studies that reported values in the range of 6-24%.[208,209] Malignant extradural spinal cord compression (SCC) may cause pain (local or radicular), weakness, sensory disturbance and/or sphincter dysfunction. The loss of neurologic function may be irreversible and patients with paralysis either at presentation or post-treatment have a shorter life expectancy.[210,211] In general, there were very few papers of high methodologic quality dealing with the emergency treatment of malignant SCC. Two randomized trials in mixed patient populations which included MM showed that dexamethasone is effective on neurologic symptoms and pain.[212,213] An evidence-based guideline for the emergency treatment of malignant SCC confirmed the efficacy of high-dose dexamethasone.[210] Radiotherapy is also effective in controlling back pain.[214,215]

Radiotherapy is less useful if a vertebral collapse is the cause of the spinal cord compression. Surgical decompression, such as posterior laminectomy, can be effective in MM patients with neurologic symptoms of spinal cord compression,[216] especially if caused by a vertebral collapse. A clinical improvement was also noted in 82% of the patients refractory to the previous radiotherapy,[217] however, laminectomy has a mortality rate of 6-10% and did not prove superior to radiotherapy.[218,219] In general, recovery of neurologic functions after treatment is mainly dependent on pretreatment levels: only 30% of non-ambulatory patients and 2-6% of paraplegic ones regained the ability to walk.[215,22] Thus,

patients should be aggressively screened and educated about SCC.[210]

Kyphoplasty is a new vertebroplasty technique in which cement is percutaneously introduced to produce vertebral augmentation: it involves the insertion of a balloon-like inflatable bone tamp into the vertebral body and the creation of a cavity, followed by insertion of a thick viscous cement into the preformed cavity. In a prospective study of 18 MM patients, kyphoplasty restored 34% of the height loss without relevant complications[221] and with a significant improvement in the patients' functional status.[222]

Recommendations

MM patients with spinal cord compression should immediately receive high-dose dexamethasone therapy (grade A). If spinal cord compression is due to bone fragments (and not to myeloma protruding masses) patients should also undergo surgery (grade B). Those patients who have neurologic impairment (deficits and/or symptoms) should also receive local radiotherapy (grade C). Candidates for surgery should receive radiotherapy postoperatively, once healing has occurred (grade C). Patients should be aggressively screened and educated about spinal cord compression (grade C). Patients with impending bone fractures of the hip or long bones should receive surgery (grade C).

Hyperviscosity syndrome

Less than 2% of the MM patients present with hyperviscosity at diagnosis and a few more develop it afterwards.[223,224] Clinical manifestations of hyperviscosity include mucosal hemorrhage, visual abnormalities along with neurologic and cardiac features such heart failure, seizures, vertigo, and diploplia. Serum viscosity levels do not correlate well with the patients' symptoms or clinical signs. Venous dilatation and retinal hemorrhage are evident at fundus oculi examination. These findings are more important than the viscosity level in evaluating the patient. It should be noted that hyperviscosity may not be correlated with the amount of circulating M protein, but usually the MC concentration is > 40 g/L.[225] The treatment of hyperviscosity is aimed at preventing complications such as bleeding, loss of vision and irreversible neurologic impairment. Automated plasma exchange requires replacement of about two-thirds of the patient's plasma volume with 5% human albumin solution or an equal mixture of albumin and 0.9% normal saline.[226,227] The procedure induces a dramatic response soon after the first plasma exchange session.[228] Therapeutic apheresis procedures are relatively safe, with a 3% to 4% overall incidence of adverse effects that are mostly reversible.[229,230] It is important to repeat the procedure at scheduled intervals, generally on a daily basis for 3 to 5 days until the hyperviscosity has been corrected and chemotherapy is initiated. In the absence of other treatments, cessation of plasma exchange treatments will result in a recurrence of symptoms within 2-3 weeks.[231] The evidence on the efficacy of plasma exchange in MM is limited to case series,[232-234] but the American Society of Apheresis has provided consensus-based recommendations for its use to treat symptomatic hyperviscosity in MM patients.[227]

Recommendations

MM patients with symptomatic hyperviscosity should be treated with plasma exchange until definite therapy can be initiated (grade C). Plasma exchange (3-4 liters) replaced with albumin 5% should be repeated at scheduled intervals until symptoms disappear (grade C). Chemotherapy should be started promptly once hyperviscosity has been stabilized by plasma exchange.

Infections

Infections are a primary cause of death in MM patients: the risk increases during induction chemotherapy, after autologous and allogeneic SCT, and during long-term maintenance with steroids. A randomized, controlled trial showed that intravenous immunoglobulin prophylaxis protected against life-threatening infections and reduced the risk of recurrent infections.[235]

The Panel deemed that CDC and IDSA guidelines on prophylactic vaccinations and the use of antimicrobial agents in neutropenic cancer patients were applicable to MM patients.[236,237] Use of antibiotic prophylaxis is not routine except for the use of trimethoprim-sulfamethoxazole to prevent *Pneumocystis carinii* pneumonitis because of emerging antibiotic resistance. Admission for intravenous antibiotic therapy is usually needed for severe systemic infection. Despite the limited immunogenicity of vaccines against *Streptococcus pneumoniae* and *Haemophilus influenzae* type B (HiB) in autologous and allogeneic transplant recipients, these vaccines are recommended because the majority of such patients have low levels of antibodies to capsular polysaccharides after transplantation. In particular, allogeneic recipients with chronic GVHD are at an increased risk of infection from encapsulated organisms (i.e., *Haemophilus influenzae* type B, *Streptococcus pneumoniae*, *Neisseria meningitidis*). Seasonal influenza vaccination is safe for MM patients, 20% of whom develop protective immunity.[238] It can be estimated from translated evidence that influenza vaccination has the potential to reduce the rates of severe respiratory illness and related mortality by 50% in patients achieving protective immunity.[237,239] An Italian trial randomized 50 MM patients to receive or not influenza vaccination. Upper respiratory illness occurred in 32% versus 72% of the vaccinated or not vaccinated patients, respectively; moreover, the mean durations

of febrile respiratory episodes and hospitalizations, and the number of non-programmed medical consultations were lower in the vaccinated patients.[240]

Recommendations

Routine use of intravenous immunoglobulins (IVIG) is not recommended as a general prophylaxis for bacterial infection in MM patients: this therapy is reserved to patients with recurrent infections and polyclonal hypogammaglobulinemia or to recipients of allogeneic grafts who experience severe hypogammaglobulinemia within the first 100 days after the transplant (grade C).

The initial IVIG dose should be 0.4 g/Kg every 3-4 weeks to reach serum IgG levels greater than 500 mg/dL. The dose should then be individualized to maintain serum IgG concentrations greater than 500 mg/dL (grade B).

Data are insufficient to recommend the use of prophylactic antibiotics during conventional chemotherapy-induced neutropenia. However, trimethoprim-sulfamethoxazole is recommended to prevent Pneumocystiis carinii pneumonia in patients receiving high-dose dexamethasone. Prophylactic antibiotics or antiviral agents should be provided to SCT recipients, according to generally accepted guidelines (CDC).

Evidence is insufficient to recommend the use of Streptococcus pneumoniae and Haemophilus influenzae type B (Hib) vaccines in all the MM patients receiving conventional chemotherapy (grade B).

HiB vaccination should be offered to autologous and allogeneic SCT recipients at 12, 14 and 24 months after transplantation, independently of the recipients' age (grade B). The currently available 23-valent pneumococcal polysaccharide vaccine is recommended at 12 and 24 months after SCT: the second dose provides a further chance to patients who failed to respond to the first one (grade B).

Seasonal influenza vaccination is recommended to all MM patients. SCT recipients should continue seasonal vaccination lifelong, beginning before the transplant and resuming 6 months after it. Family members and close or household contacts of allogeneic SCT recipients should also receive seasonal influenza vaccination before transplantation and for 2 years thereafter (grade B).

Amyloidosis

Light chain amyloidosis (AL) occurs in approximately 12 to 15% of patients with MM. Patients with MM and AL amyloidosis are definitely more fragile than patients with only MM because of the several and/or severe organ dysfunctions. Controlled studies suggest that treatment with melphalan and prednisone may provide a marginal survival benefit.[241] Autologous SCT may offer potential for long-term benefit,[242] and although patients are highly selected, response rates can approach 60%.[243,244] The TRM of autologous SCT is over 20% even in centers with particular experience of the procedure, thus accurate selection of patients is necessary to limit the TRM.[242] Stem cells should be collected even in patients temporarily not candidates for SCT, but with a forseeable improvement in organ function. In those patients with a potentially reversible contraindication to ASCT, high-dose dexamethasone[245] should be employed in order to preserve the bone marrow stem cells. After harvesting or in patients definitely not candidates for autologous SCT, high response rates can be achieved with the association of melphalan 0.22 mg/Kg plus high-dose dexamethasone 40 mg given orally on days 1-4 every 28 days.[246] Patients who are not eligible for high-dose dexamethasone (i.e. those with refractory ventricular arrhythmias, gastro-intestinal bleeding, or psychosis) should be treated with standard MP. Refractory or relapsing patients can be treated with intermediate dose dexamethasone (20 mg orally on days 1-4, every 21 days) and thalidomide (starting from 100 mg/day and up to 200 mg/day). Thalidomide has been shown to be effective in AL patients, but poorly tolerated.[247-249] Dangerous bradycardia may occur during thalidomide therapy, and therefore dynamic ECG monitoring (Holter) is recommended monthly during thalidomide treatment.

Recommendations

AL amyloidosis in MM patients below 60 years old should be treated with high-dose chemotherapy followed by SCT provided that the patient has no more than 2 organs involved and does not have severe heart involvement (grade B).

In patients aged between 60 and 65 years old and with a serum creatinine equal to or greater than 2 mg/dL (173 mmol/L), the procedure should be considered with caution and the melphalan dose should be reduced to 100 mg/m^2 (grade D).

Stem cell harvesting at diagnosis should be considered also in those patients who are initially ineligible for autologous SCT, but who do not have severe heart failure (i.e. their NYHA class is I or II), symptomatic hypotension or recurrent syncope, since these patients can tolerate the cell harvesting procedure and may subsequently become eligible for autologous SCT. These patients should avoid melphalan before stem cell harvesting. After harvesting, patients can be treated with oral melphalan (0.25 mg/Kg) plus oral high-dose dexamethasone (40 mg) for 4 days, every 28 days (grade C). Patients who are not eligible for high-dose dexamethasone should be treated with standard MP.

Refractory or relapsing patients can be treated with intermediate dose dexamethasone (20 mg orally, 4 days every 21 days) and thalidomide (from 100 mg/day up to 200 mg/day) (grade D). Monthly Holter monitoring is recommended during thalidomide therapy in order to detect dangerous bradycardias promptly (grade D).

Plasmacytoma

Solitary bone plasmacytoma (SBP) and extramedullary plasmacytoma (SEP) are rare plasma cell proliferative disorders. The diagnosis of plasmacytoma is based on histologic confirmation of monoclonal plasma cell infiltration of a single disease site and on the exclusion of systemic MM. SBP accounts for about 5% of all plasma cell disorders.[1] It is often localized in the spine (25-60% of the cases) and over 40% of the patients have spinal cord compression.[250-252] Local radiotherapy achieves remission in over 86% of the cases in a median time of 5 months,[253,254] normalizes the MC levels in 20-50% of patients,[253,255] and allows recovery from neurologic impairment and symptom relief.[253,256] The efficacy of radiotherapy has only been assessed in non-comparative retrospective studies: local recurrence occurs in 3-26% of the patients within the first 5 years after radiation,[257,258] whereas no recurrence was reported in small series of patients treated with more than 35-40 Gy.[259,260] Doses above 50-70 Gy are potentially toxic to the spinal cord and are usually avoided. The median OS time of patients treated with radiotherapy is 10 years.[256]

Transformation to MM occurs in 20% of the cases within one year from diagnosis and in 50% by 10 years,[250,257,258,261-263] but may occur even 13 years after diagnosis.[258] Anterior laminectomy, vertebroplasty and kyphoplasty are useful in patients with vertebral instability or bone particles compressing the cord.[221,261] Patients with an unsuspected marrow lesion,[264] and/or persistence of MC after radiotherapy[263] are at a greater risk of progression. However, most patients whose plasmacytoma transforms to MM probably had a systemic multifocal disease not revealed by standard X-ray imaging but possibly identifiable by MRI and PET.[265,266] A randomized trial[267] and other controlled studies[268,254] showed a certain survival benefit from prophylactic chemotherapy, however, other studies did not.[257,269,270]

SEP accounts for 3-4% of all plasma cell disorders and is often localized in the upper aerodigestive tract. The prognosis of patients with SEP appears to be better than that of patients with SBP because approximately 70% of patients with SEP remain disease-free at 10 years.[271] Radiation therapy to the target area and adjacent lymph nodes can achieve local control in more than 80% of the cases, especially if they are small size tumors with a low-to-intermediate histologic grading.[253,254] Relapse in regional lymph nodes is frequent only in those patients not receiving radiation to the nodes.[254,272] Surgery can also achieve very good results in the case of SEP of the aerodigestive tract, especially if the resection potential is good.[255] Combined radiation and surgery have better results when complete surgical tumor resection is doubtful or impossible and/or if lymph node areas are affected.[254] Local recurrence occurs in approximately 20% of SEP, while progression to MM occurs in less than 20% of the patients.[255,264,273] Overall the 5-year OS is 40% for pulmonary location[274] and 60-82% for head-and-neck locations.[275,276] Only one level 2- study verified the impact of prophylactic chemotherapy in this setting and found no advantage on either relapse rate or PFS.[268] More recently, Dimopoulos *et al.*[271] also concluded that there is no role for systemic chemotherapy in the management of SEP or SBP.

Recommendations

Local radiotherapy is the treatment of choice for newly diagnosed solitary bone plasmacytoma and primary extramedullary plasmacytoma: 45-50 Gy should be provided to the involved field, including a margin of normal tissue (grade C).

Surgery is recommended for patients with solitary bone plasmacytoma with vertebral instability or for fixation of a long bone (grade D) and for patients with extramedullary plasmacytoma of the upper aerodigestive tract which has a good resection potential (grade D). Prophylactic chemotherapy is not recommended (grade B). After radiotherapy, patients should have twice yearly monitoring of serum and urine electrophoresis and immunofixation, serum calcium and creatinine and full blood count (grade D). Skeletal X-rays should be performed at least once a year and when patients are symptoms (grade D).

Discussion

The present guidelines are based on the most updated and comprehensive review of literature on MM therapy. This literature provided the basis for evidence to be translated into therapy recommendations. The consensus methodology was employed with caution and consensus-based statements are explicitly marked with a D grade. Indeed, the Expert Panel deemed it appropriate to fill some evidence gaps, providing recommendations based on indirect evidence and personal experience, after a methodologically constrained discussion.

Comparisons with currently available guidelines are shown in Table 2 and Table 3.[277-286] All the published guidelines agree on the criteria to start therapy and on the usefulness of autologous SCT as a frontline therapy, however, the cutoff age to undergo autologous SCT varied. The guidelines also concurred on two major aspects of autologous SCT: the source of stem cells (peripheral blood unpurged stem cells) and the use of high-dose melphalan without TBI. Regarding first-line standard chemotherapy, all the guidelines agreed that oral melphalan was a well consolidated and effective strategy, however, some guidelines recommended the association with prednisone or prednisolone (Table 2). Most of the guidelines indicated alternative options to melphalan, such as MP-based combination chemotherapy,

cyclophosphamide or high-dose dexamathasone plus thalidomide. IFN-α was not accepted as a standard maintenance therapy after conventional chemotherapy by any of the guidelines due to its low clinical benefit, negative impact on quality of life and high cost. Front-line allogeneic SCT for the younger patients was usually considered as an experimental option, due to the high TRM. Non-myeloablative SCT was considered a valuable experimental option, too, since the guidelines deemed that it was worth further studies before being implemented in clinical practice.

A few guidelines systematically addressed second-line therapies but only the present one provides extensive recommendations on thalidomide use in relapsed and/or refractory patients. Finally, the present guidelines are the only ones to address therapies for all the relevant complications of MM: in particular they are the only guidelines providing recommendations on the management of MM-related amyloidosis.

Despite the evidence-based nature of most of the recommendations, there are intrinsic limitations in the process of translating evidence into practice recommendations.[287] In particular, the trade-offs between toxicity and uncertain benefit (e.g. allogeneic SCT) or between quality of life and survival prolongation are subjective in nature and may be changed by incoming studies. Secondly, equivalence between therapies is sometimes implicitly assumed (i.e. between different bisphosphonates for bone lesions) despite no trial being adequately powered and designed to test an equivalence hypothesis or there being no head-to-head trial. Finally, some recommendations are based on indirect evidence, intermediate outcomes or experts' opinion and may therefore be inconsistent with future pieces of evidence. These uncertainties are explicity declared in the recommendations, whose grading score is mainly related to these uncertainties. Moreover, the present guidelines do not stress financial or psychological issues of MM therapy. Indeed, some expensive therapies, such as autologous SCT,[288,289] have been reported to be cost-effective,[290,291] while others, such as IFN-α, are not.[292,293]

More than 60 relevant papers have already been published since the last meeting of the Expert Panel. Therefore, the present guidelines are intended to be valid for the next 2 years, after which they will require a revision.

Addendum: Literature review up to 31 December 2003

Since the present guide-lines were based on a systematic review of literature published up to 31st May, 2003, a further analysis of data published since that date up to 31st December 2003 was performed before publication of the paper. We found 5 randomized controlled studies dealing with therapy of MM published in full and we selected 3 randomized trials presented in abstract form during the 2003 ASH Meeting.

To investigate whether combination chemotherapy with vincristine, cyclophosphamide, prednisolone, and melphalan (COP/ MP) with the addition of ranimustine (MCNU) (MCNU-COP/MP) is superior to the slightly modified COP/MP (mCOP/MP) regimen in MM, in a multicenter randomized study 210 patients with newly diagnosed, overt MM not treated with chemotherapy were randomized to receive either MCNU-COP/MP or mCOP/MP.[294] The response rate to mCOP/MP was 43.7% and that to MCNU-COP/MP was 56.1% ($p = 0.097$). The progression-free survival (PFS) was significantly longer for patients treated with MCNU-COP/MP than for patients treated with mCOP/MP (median, 23.0 months versus 15.8 months, $p = 0.014$). No significant difference in overall survival rate was observed between the groups (median, 49.9 months versus 44.0 months, $p = 0.75$). In conclusion, the study documented that addition of MCNU to mCOP/MP has no benefit on survival.

Ninety patients with untreated, stage I-II A myeloma, were randomized to receive or not monthly infusions of pamidronate for 1 year, without additional therapies.[295] Three years after the start of the treatment, the disease had progressed in 25% of pamidronate-treated patients and in 26.8% of controls (p = n.s). Among the 21 patients who required chemo-radiotherapy, skeletal events developed in 9/11 (81.8%) controls and in 4/10 (40%) of treated patients ($p < 0.01$). Patients with advanced breast carcinoma or MM (n = 1648) were randomized to receive 4 mg or 8 mg (reduced to 4 mg) zoledronic acid as a 15-minute infusion or to receive 90 mg pamidronate as a 2-hour infusion every 3-4 weeks for 24 months.[296] In patients with MM, after 25 months of follow-up, zoledronic acid reduced the overall proportion of patients with a skeletal event and reduced the skeletal morbidity rate to a similar degree as pamidronate.

A prospective randomized study was designed to compare the objective response rates of two VAD-like outpatient regimens as primary treatment for symptomatic patients with MM.[297] One hundred and twenty-seven patients received a VAD *bolus*, which consisted of vincristine 0.4 mg i.v., doxorubicin 9 mg/m^2 i.v. and dexamethasone 40 mg p.o. daily for four consecutive days and 132 patients received VAD *doxil*, which consisted of vincristine 2 mg i.v. and liposomal doxorubicin 40 mg/m^2 i.v. on day 1 and dexamethasone 40 mg p.o. daily for 4 days. The two regimens were administered every 28 days for four courses and in courses 1 and 3, in both arms, dexamethasone was also given on days 9-12 and 17-20. An objective response was documented in 61.4% and 61.3% of patients treated with VAD *bolus* and VAD *doxil*, respectively. The results indicated that both VAD *bolus* and VAD *doxil* can be administered to outpatients and can provide an equal opportunity of rapid response in many patients with MM.

Table 2. Comparison of currently available guidelines for front-line multiple myeloma treatment.

	UK-MF[277]	*CCO-PGI*[278]	*FMSD*[279]	*BCCA*[280]	*NCCN*[281]	*ASBBMT*[282]	*IMF*[283]	*Present guideline*
Date of publication	Oct 2002	Oct 2002	Dec 2001	May 2000	2001	Jan 2003	May 2003	
Evidence collection	June 2001	April 2000	n.a.		n.a.	June 2002	n.a.	March 2003
Grading of evidence	yes	yes	yes		yes	yes	no	yes
Candidates for *watch and wait*								
Asymptomatic pts^	All	n.a.	All	Selected^^	All	All	All	Selected^^^
Front-line standard dose chemotherapy								
Not candidates for ASCT	Mel, MP; Ctx; ABCM°	Mp or combination Cht	MP or Mp	Mp°	Mp, VPMCP, VAD, VBAP	n.a.	MP; VAD, thalidomide + HD-Dex, Cytoxan, VAD-based	Mp°
Candidates for ASCT	VAD-like	VAD-like	n.a.	Not Mp	Not alkylating agents or nitrosureas	n.a.	VAD, thalidomide + HD-Dex, Cytoxan	VAD×4
Renal failure	VAD, HD-Dex	–	n.a.			n.a.		HD-Dex and VAD-based chemotherapy
Maintenance with IFN-α	Effective but not cost-effective	–	n.a.	Not recommended	Equivalent to steriods or no maintenance	n.a.	In clinical trials (steroids are an option)	Possible option +/- steroids
Front-line autologous stem cell transplantation								
Candidates cut-off age		60/70 yrs[§]	<55/60 yrs	<65-70 yrs	n.a.[§]	Preferred as early therapy	<70 yrs	<65/70 yrs
Excluded if renal failure		No	Yes	–	–	–	No	No
Other exclusion criteria		Low performance status					Severe comorbidity	
Source of stem cells	–	Peripheral	–		–	Peripheral	Peripheral	Peripheral
Purging of stem cells	No	In clinical trials	–		–	No	No	No
Selection of stem cells	–	Insufficient data	–		–	Insufficient data	–	No
Preparative regimen	Mel 200	Mel200			+/- TBI[§§]	Melphalan (no TBI)	Mel200	Mel200
Maintenance IFN-α		Effective but not cost-effective	No consensus		In clinical trials	Insufficient data	In clinical trials	In clinical trials
Tandem transplantation		In clinical trials	No standard use			Insufficient data	In clinical trials	Recommended
Allogeneic stem cell transplantation								
Front-line allogeneic SCT (from sibling donor)		To be considered*	Inferior to autologous SCT at present: not recommended routine		In clinical trials[#]	Less preferred than autologous SCT	To be considered in the younger patients[##]	In clinical trials[###]
Syngeneic SCT		n.a.			n.a.	n.a.	Recommended up to 65 years	Recommended
Non-myeloablative allogeneic SCT		In clinical trials	n.a.		n.a.	In clinical trials	In clinical trials	In clinical trials
DLI		Persistent or progressive disease	n.a.		Feasible option	n.a.		Relapsed or progressed disease

UK-MF: United Kingdom Myeloma Forum; CCO-PGI: Cancer Care Ontario Practice Guideline Initiative; FMSD: Finnish Medical Society Duodecim; NCCN. National Cancer Care Network; IMF: International Myeloma Foundation; BCCA: British Columbia Cancer Agency; MP: oral melphalan + prednisolone; Mp: oral melphalan + prednisone; Mel200: melphalan 200 mg/m²; Mel140TBI : melphalan 140 mg/m² plus total body irradiation; ^ no related organ damage nor symptoms; ^^asymptomatic and without urinary; Bj: <2 bone lesions; stable MC: ^^^ without chromosome 13 deletion. §Preferred option for some patients not progressing during first-line chemotherapy and with sufficient renal, cardiac or liver function; §§TBI-free preparative regimens should be used for those patients who have received previous radiotherapy Up to 50 years of age # Younger patients with responsive or stable disease after primary chemotherapy; ###Patients with chromosome 13 deletion and age <50 years ## with a CMV negative HLA-matched donor ° until plateau.*

Table 3. Comparison of currently available guidelines for supportive multiple myeloma therapy.

	UKMF[277]	*BCCA*[280]	*NCCN*[281]	*IMF*[283]	*ASCO/ASH*[284,285]	*Present guidelines*
Date of publication	October 2002	May 2000	2001	May 2003	October 2002	
Evidence collection	June 2001		n.a.	n.a.	January 2002 (bisph) Dec 2000 (epoetin)	March 2003
Intravenous immunoglobulins	Possible utility		To be considered if recurrent life-threatening infections	May be a helpful infections adjuntive and polyclonal measure in management of infections	n.a.	Severe recurrent hypogamma globulinemia§
Plasma exchange	Recommended for hyperviscosity syndrome		May be considered for hyperviscosity syndrome	n.a.	n.a.	Recommended for hyperviscosity syndrome
Bisphosphonates	Clodronate or pamidronate recommended for all MM pts Intervanous bisphosphonates for hypercalcemia	Pamidronate until active treatment of MM is abandoned#	In all patients with bone lesions or osteopenia and/or hypercalcemia	To treat hypercalcemia	Long-term pamidronate or zoledronic acid in patients with bone lesions or ostheopenia	Long-term clodronate, pamidronate or zoledronic acid to patients with bone lesions or severe osteopenia
Erythropoietin	Symptomatic anemia or chronic renal failure			Persistent symptomatic anemia	Persistent anemia (Hb<10g/dL) despite chemotherapy	Hb<10 g/dL

§or undergoing allogeneic SCT from unrelated donor and presenting severe hypogammaglobulinemia within the first 1000 days post-transplant; #reduce dosage after two years.

The efficacy of intensified chemotherapy followed by myeloablative therapy and autologous stem cell rescue was compared with that of intensified chemotherapy alone in 261 patients younger than 66 years newly diagnosed with stage II/III disease MM.[298] Patients were randomized after remission induction therapy with VAD to receive intermediate-dose melphalan (IDM) without stem cell rescue (n = 129) or the same regimen followed by myeloablative therapy consisting of cyclophosphamide, total body irradiation, and autologous stem cell reinfusion (n = 132). Interferon-α-2a was given as maintenance treatment. Of the eligible patients, 79% received both cycles of IDM and 79% of allocated patients actually received myeloablative treatment. The response rate (complete remission plus partial remission) was 88% in the intensified chemotherapy group versus 95% in the myeloablative treatment group. Complete remission was significantly higher after myeloablative therapy (13% versus 29%; $p = 0.002$). With a median follow-up of 33 months (range, 8-65 months), the event-free survival was not different between the two treatment groups (median 21 months versus 22 months; $p = 0.28$). Time to progression was significantly longer after myeloablative treatment (25 months versus 31 months; $p = 0.04$). The overall survival was not different (50 months versus 47 months; $p = 0.41$). The conclusion of the trial was that intensified chemotherapy followed by myeloablative therapy as first-line treatment for MM resulted in a higher CR and a longer time to progression than did intensified chemotherapy alone, without a better EFS and OS.

The ECOG, CALGB and SWOG enrolled 899 patients with newly diagnosed MM to receive VAD induction × 4 cycles (n=805), followed by randomization to a single PBSC-supported HDT (n=258) vs VBMCP (n=252).[299] Responders to VBMCP or HDT were randomized to receive or not IFN. Response rates were similar with HDT/VBMCP. Progression-free survival was superior after HDT (25 vs 21 months, $p = 0.05$).

With the aim of comparing HDT/SCT versus continued conventional chemotherapy in MM patients responding to the initial treatment (4 courses of alternating BVMCP/VBAD), 216 patients were randomized to receive 8 additional courses of BVMCP/VBAD or intensification with HDT/HSC, melphalan 140mg/m^2/TBI or melphalan 200 mg/m^2.[300] Complete response, i.e. negative electrophoresis, was significantly higher in the HDT/SCT arm (30% vs 11%). However, PFS was not significantly different between recipients of HDT/SCT and conventional chemotherapy. Preliminary results of the two protocols (IFM9903 and IFM 9904) comparing autologous followed by miniallogeneic transplantation and double

autologous transplant in high-risk *de novo* MM patients showed that both strategies lead to survival rates superior to 50% at 3 years on an intent-to-treat basis.[301] The strength of evidence was in no case sufficient to question the validity of the recommendations of these guidelines.

After submission of the paper, author-based recommendations for the treatment of MM and guidelines on the diagnosis and management of solitary plamacytoma of bone and solitary extramedullary plasmacytoma have been issued.[302-303]

All authors provided substantial contributions to the conception and design of these guidelines and to the analysis and interpretation of data, in particular during panel meetings. All authors also participated in drafting the article and revising it critically, and gave final approval of the version to be published. GB and MM were responsible for the project's design and analysis of results. The authors thank Giuseppe Longo, for his valuable support in literature revision, and Cristina Azzan, for her precious contribution to the electronic repository of full-paper articles. The authors are indebted to Dompè Biotec for providing the support necessary to conduct the Consensus Conferences and the whole project.

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