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State of the art therapy in multiple myeloma and future perspectives

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ABSTRACT

Treatment for multiple myeloma (MM) has changed beyond recognition in the past decades. While until the early 1980s, MM caused a slow progressive decline in quality of life until death after about two years, today's patients can expect a 50% chance of achieving a complete remission, a median survival time of five years and a 20% chance of surviving longer than ten years. State of the art therapy comprises: evidence-based supportive care; highly effective and well tolerated chemotherapeutic regimens; and for patients qualifying for intensive high-dose conditioning, autologous haematopoietic stem cell transplantation (HSCT) is an option. Maintenance therapy has become increasingly important since a majority of patients is able to achieve a good remission after front-line therapy which is aimed to be preserved as long as possible. In addition, improved understanding of the disease biology has led to the development of novel biological treatment agents, such as thalidomide, bortezomib and others, targeted at cellular mechanisms and interactions, e.g. with the bone marrow microenvironment. These strategies are incrementally integrated into modern MM care. This review considers recent clinical advancements in anti-myeloma strategies and provides an overview of the state of the art management of MM patients.

1. Introduction

MM is a malignant disorder characterized by an uncontrolled clonal proliferation of malignant plasma cells which normally produce a monoclonal paraprotein. In the majority of patients, the paraprotein is readily detectable in the serum and urine. Especially at later stages, MM may induce lytic bone lesions, renal function impairment and immunodeficiency caused by myelosuppression. With effective treatment, the median overall survival (OS) is approximately four years.

The central goal in improving MM treatment is the achievement of prolonged complete remission (CR) rates, long-term OS, and improvement in quality of life, with few MM-associated symptoms and with as few treatment cycles as possible. Over the last years, high-dose (HD) chemotherapy (CTx) followed by autologous peripheral blood stem cell transplantation (auto-PBSCT) has emerged as one effective approach to reach this objective.[1] Auto-PBSCT given with need for treatment after standard-CTx or early during the treatment course (at initial diagnosis) has been demonstrated to be very profitable in MM.[2] In patients with advanced disease and adverse prognostic factors, such as cytogenetic abnormalities, the therapeutic approach of an auto-, followed by an allogeneic (allo)-SCT is currently pursued in clinical trials.[3] Allo-SCT has been shown to be potentially curative for MM patients, although long-term results have to be awaited. The introduction of reduced intensity conditioning (RIC) regimens has decreased treatment-related morbidity and mortality (TRM) considerably.[2–4] The current use of earlier auto-PBSCTs, tandem transplants within clinical trials, and implementation of novel

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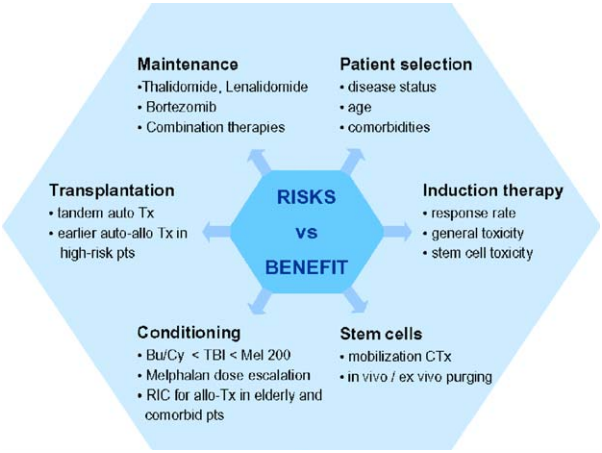

Fig. 1 – Hexagon of treatment considerations, improving outcome and patient safety. Abbreviations: TBI: total body irradiation, BuCy: Busulfan/Cyclophosphamide regimen, RIC: reduced intensity conditioning.

anti-MM drugs used upfront, as part of the HD-conditioning regimen or maintenance treatment, gives hope to improve the management of MM further. With increasing success, these more intensive treatment strategies are also used in older patients, which can be attributed to advances in reduced intensity conditioning and supportive care measurements.

Treatment considerations to improve the outcome and safety in MM patients are depicted in Fig. 1, and include optimal patient selection for highly effective and well-tolerated induction and conditioning regimens, single vs. multiple transplants, cell therapy issues, novel anti-MM drugs and maintenance therapy approaches.

2. To treat or not to treat

Criteria that aid the classification of MGUS, asymptomatic (smoldering) versus (vs.) symptomatic and non-secretory MM, as well as of solitary-, extramedullary- and multiple solitary-plasmocytomas have been defined by the 'International Myeloma Working Group':[5] MGUS shows a monoclonal protein <30 g/l, bone marrow (BM) clonal plasma cells <10% and no evidence of MM, other B-cell proliferative disorders or amyloidosis. In asymptomatic MM, the M-protein is $\geqslant$30 g/l and/or clonal BM plasma cells $\geqslant$10%, but no related organ or tissue impairment (ROTI). Symptomatic MM shows the pathologic findings as described for asymptomatic MM and ROTI, which is typically manifested by hypercalcaemia, renal

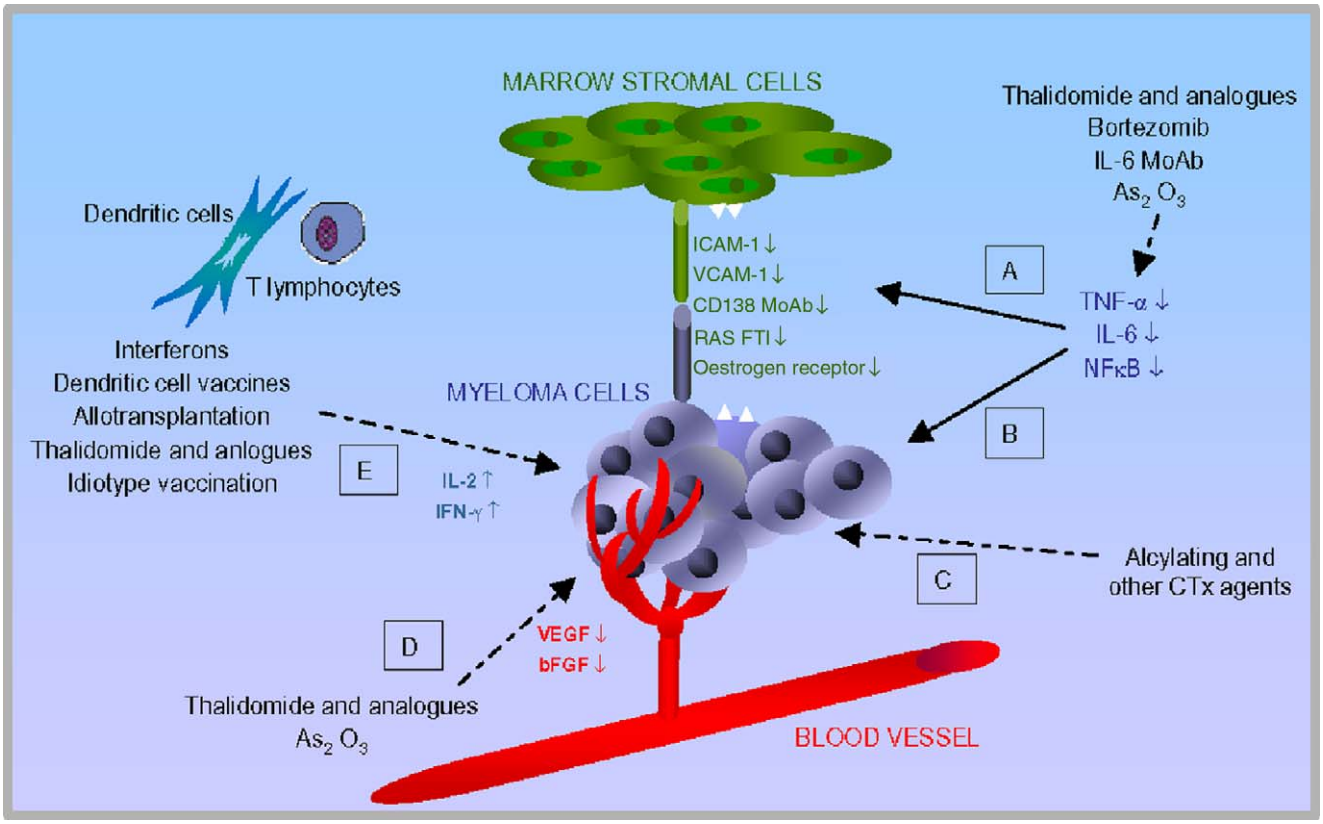

Fig. 2 – Targets of myeloma treatment. Changes of microenvironment by reduction of TNF-I, IL-6 and indirectly NFκB lead to A) impaired interaction of myeloma and stromal cells and B) induction of apoptosis in myeloma cells. C) Direct cytotoxic effect. D) Antiangiogenic effect. E) Stimulation of immunological effect versus myeloma cells.
***Abbreviations*: MoAb – monoclonal antibody. As_2O_3 – arsenic trioxide. TNF-I – tumor necrosis factor alpha. IL-6 – Interleukin-6. NFκB – nuclear factor kappa B. ICAM-1 – intercellular adhesion molecule 1. VCAM-1 – vascular cell adhesion molecule. FTI – farnesyl-transferase inhibitor. VEGF – vascular endothelial growth factor. bFGF – basic fibroblast growth factor. IL-2 – Interleukin-2. IFN-γ – Interferon gamma. Solid arrows indicate stimulation or secretion and dashed arrows inhibition.**

Table 1 – Investigations to aid diagnosis of multiple myeloma

Site and test	What to look for
Medical history and physical examination	
Blood/Serum	
Immunoelectrophoresis/immunofixation	Paraprotein or "M" component (53% IgG, 20% IgA, rarely IgM), serum viscosity
Immunoglobulin profile	Immunoparesis
β2 microglobulin	High (>2.5 mg/l)
Serum free-light-chain assay	Elevated level and altered κ:λ ratio
Hematology	Low platelet and hemoglobin concentrations, high ESR, plasma cells in peripheral blood
Biochemistry	Elevated creatinine, urea, uric acid, LDH, C-reactive protein, calcium, total protein
Urine	
Immunoelectrophoresis/immunofixation	Bence-Jones protein (20% light chain disease)
Bone marrow	
Aspirate	Plasma cells, morphology, cytogenetics, FISH
Trephine - histology	Cellularity, amyloid, MVD (angiogenesis)
Bones/whole body	
Skeletal survey	Lytic lesions, fractures
CT/MRI/PET	Plasmocytoma lesions, correlation with skeletal survey
Serum amyloid protein (SAP)	Amyloid load scan
DEXA scan	Osteoporosis, bone healing

Abbreviations: ESR: erythrocyte sedimentation rate; LDH: lactate dehydrogenase; FISH: fluorescence in-situ hybridisation; MVD: microvascular density; DEXA: Dual energy X-ray absorptiometry.

insufficiency, anaemia or bone lesions (CRAB). Non-secretory myeloma is characterized by the absence of M-protein in the serum and urine, BM plasmocytosis and ROTI (see Fig. 2).

To precisely define these distinct myeloma entities, investigations as summarized in Table 1, aid to distinguish between MGUS and symptomatic MM and related disorders, and thereby allow the well-timed initiation of treatment. MGUS and Stage I MM require no specific anti-myeloma therapy, but, possibly already at these early stages, supportive care may be of advantage to be used regularly. These supportives in early stage disease may also comprise osteoprotective drugs, such as Bisphosphonates (which are for stage I disease tested in clinical studies) and Vitamin D3 plus Calcium. Stage II and III MM patients definitely require osteoprotective supportives.

Since there is also an increased need for better identification of prognostic parameters on which therapeutic stratifications are based, Greipp and colleagues have introduced the International Staging System (ISS) for MM.[6] This ISS is based on serum albumin and β2-microglobulin and may be useful for determining prognosis and identifying appropriate treatment strategies. In terms of diagnostic improvements, cytogenetic, genomic and proteomic analyses have already, or for the latter will become powerful tools in predicting disease outcome of MM patients, should offer a comprehensive source of novel targets for specific anti-MM treatment strategies, and may facilitate inclusion into innovative treatment strategies and clinical trials.

3. Induction therapy

Prior to ASCT, induction therapy allows the collection of PBSC and with responsive disease may further improve transplant results ('*in vivo* purging'). Alkylating agents, especially their prolonged usage (e.g. $\geqslant$6 cycles of previous chemotherapies), dense bone marrow infiltration, prior irradiation, advanced age, and possibly also elevated plasma viscosity (interfering with the gradient at leukapheresis and/or Ig-coated CD34+ cell that might be less efficiently separated) are factors impairing stem cell harvests and engraftment. [7–9] If ASCT is anticipated, long alkylating agent use should be avoided in particular, since PBSC collection results may decline considerably.[7] In addition, the use of alkylating agents prior to PBSC collection increases the risk of MDS post-transplant.

VAD (vincristine, adriamycin, dexamethasone) chemotherapy has been widely used as an induction regimen, nevertheless PBSC are better mobilized with other regimens, such as IEV (Ifosphamide, Etoposide, Doxorubicin), CEV (Cyclophosphamide, Etoposide, Doxorubicin), or Cyclophosphamide alone.[10] While objective response rates achieved with VAD are between 40–70%, its application is demanding (due to the continuous adriamycin and vincristine application) and it requires a central line and in-patient treatment. Since response rates are similarly obtained with dexamethasone alone[11] and the latter avoids the toxicity and treatment complications of prolonged chemotherapy regimens (including the risk of secondary myelodysplasia), VAD is less frequently used.

As oral CTx regimens: Idarubicine and Dexamethasone (ID); Thalidomide, e.g. combined with Cyclophosphamide and Dexamethasone; Lenalidomide given alone or in combination protocols; and others are currently tested as summarized in Tables 2 and 3. Since Thalidomide and derivatives induce total response rates of 32% with single use, the combination with dexamethasone or others can generate substantially increased response rates. As Thalidomide and potent analogues seem to be more potent with earlier treatment initiation, these are now implemented into induction therapies. Moreover, Thalidomide doses have been lowered to 100–200 mg/d, instead of previously 400–800 mg/d, thereby minimiz-

Table 2a – Standard treatment vs. autologous stem cell transplantation (ASCT) in multiple myeloma patients

Study	# pts	Age (years; median, range)	Tx conditioning	Standard CTx	CR-rate (%) (Tx vs. Std)	EFS (Tx vs. Std)	OS (Tx vs. Std)
Attal 1996[15]	200	57 (n.g.)	140 mg/m^2 Mel + TBI 8Gy	VMCP/BVAP	22 vs 5%*	27 vs 18 (months)*	not reached vs 37 (median; months)*
Palumbo 2004[16]	194	64 (51–70)	2–3 × 100 mg/m^2 Mel	Mel/Prednisone	25 vs 6%*	37 vs 16% (3 years)	77% vs 62% (3 years)
Child 2003[1]	401	55 (33–66)	200 mg/m^2 Mel	CVDP	44 vs 8%*	31 vs 19 (months)*	54 vs 42 (months)*

Abbreviations: pts: patients; Tx: autologous transplantation; CTx: chemotherapy; Std: standard treatment; N.g.: not given; CVDP: Cyclophosphamide, Vincristine, Doxorubicin, Prednisolone.
* Significant ($P < 0.05$).

Table 2b – ASCT in multiple myeloma patients after relapse (= second line) and as first line treatment

	Study	# pts	Conditioning	CR-rate	OS
Second line	Lee 2002[55]	50	various	18%	9 months (median)
	Fermand 1998[19]	202	various	41%	64 months (median)
First line	Harousseau 1995[56]	133	Mel 140 mg/m^2	37%	46 months
	Cunningham 1998[39]	84	Mel 140 mg/m^2 +/− IFN	77%	78 months (median)
	Harousseau 1995[56]	81	Mel 140 mg/m^2 +/− TBI	27%	39 months (median)
	Attal 1992[57]	100	Mel 120 mg/ m^2 +TBI +IFN	22%	52% (60 months)
	Harousseau 1992[58]	35	Mel 140 mg/ m^2 +/− TBI	34%	41 months (median)
	Moreau 2002[59]	140	Mel 140 mg/m^2 +TBI	41%	65.8% (45 months)
	Moreau 2002[59]	142	Mel 200 mg/m^2	49%	45.5% (45 months)
	Lenhoff 2000[60]	274	Mel 200 mg/m^2	41%	71% (36 months)
	Alegre 1998[61]	259	Mel 200 mg/m^2 +/− TBI	51%	35 months (median)
	Bjoergstrand 1996[62]	189	Mel +/ − TBI +/ − Cyclophosphamide	40%	34 months (median)
	Majolino 1999[63]	290	various	40%	47% (72 months)

Abbreviations: Mel: Melphalan, TBI: total body irradiation, IFN: Interferon.

Table 2c – Single vs. tandem ASCT in multiple myeloma patients

Study	# pts	Randomized	Age (years; median)	CR-rate (%) (single vs. tandem)	EFS (months) (single vs. tandem)	OS (months) single vs. tandem)
Attal 2003[3]	399	*	52	34 vs 35	25 vs 30*	48 vs 58*
Cavo 2003[20]	220	*	<61	31 vs 43	21 vs 31*	56 vs 60
Sonneveld 2003[21]	303	*	<66	13 vs 28	20 vs 22*	55 vs 50

* Significant ($P<0.05$).

ing toxicity. [12,13] This dose may prove to be lowered further with effective combination therapies and the use of Thalidomide derivatives.

4. Transplants and conditioning

Although allo-SCT may be a potentially curative strategy in 30% of patients, cure in MM still remains rare, nevertheless, numerous approaches to improve the outcome of MM patients have been realized during the last decade. These advances consist of best patient selection for clinical trials and new treatment options, such as: repetitive transplants; auto-allo transplant procedures; implementation of RIC-allo-SCT; well-tolerated conditioning regimens for auto-PBSCT; specific and unspecific immunotherapies; maintenance treatment; and usage of all of these in concert with novel agents.

Since it is safe and effective, auto- as compared to allo-SCT has become the most common procedure in MM. Presently, only 6% of transplants in MM are allo-SCT and 94% are ASCT. This has shifted MM to be the most common indication for ASCT in the world.[14] ASCT has evolved from large randomized trials showing that HD-therapy is superior to conventional CTx. Studies, as summarized in Table 2a, demonstrated for HD-Melphalan conditioning vs. standard chemotherapy treatment an improved CR rate (22–44% vs. 5–8%) and a by 12–30 months prolonged event-free survival (EFS) and OS.[1,15,16]

Efforts of improving the outcome with HD-regimens have also been accompanied by changes in the conditioning regimens to make PBSCT an attractive treatment option for frail patients. Studies that have compared Busulfan and Cyclophosphamide (Bu/Cy) vs. HD-Melphalan (MEL200) condition-

Table 3 – Novel therapies for the treament of multiple myeloma

Novel therapy, Mechanism	Disease status	Single agent or combined regimen	Clinical Phase	No of patients	Response Rate ORR/CR	Reference
Bortezomib	Refractory/relapse	single agent	III	669	38%/6%	Richardson 2005[31]
proteasome inhibition	Refractory/relapse	thalidomide	II	79	60%/20%	Zangari 2004[64]
	Refractory/relapse	thalidomide, dexamethasone	II	13	100%/0%	Chanan-Khan 2004[37]
	Primary treatment	adriamycin, dexamethasone	II	21	95%/24%	Cavenagh 2004[65]
Thalidomide	Refractory/relapse	single agent	III	84	32%/10%	Singhal 1999[66]
immunomodulatory, antiangiogenic	Refractory/relapse	cyclophosphamide, dexamethasone	II	53	60%/na	Dimopoulos 2004[67]
	Primary treatment	dexamethasone	II	26	73%/na	Wang 2005[68]
	Maintenance	single agent	III	580	EFS at 40 months 70% vs 53%	Attal 2004[41]
Lenalidomide	Refractory/relapse	single agent	I	24	70%	Richardson 2002[69]
immunomodulatory	Primary treatment	dexamethasone	I	13	85%	Rajkumar 2004[70]
Arsenic trioxide	Refractory/relapse	single agent	II	24	33%	Hussein 2004[71]
ROS and GSH induction	Refractory/relapse	melphalan, Vitamine C	I/II	20	57%	Berenson 2004[72]
2 ME 2	Refractory/relapse	single agent	I/II	51	0%	Rajkumar 2003[73]
ROS induction, microtubule inhibition						
SAHA	Refractory/relapse	single agent	I	7	29% MR	Richardson 2004[74]
histone deacetylase inhib.						
G 3139	Refractory/relapse	thalidomide, dexamethasone	I/II	16	56%	Badros 2003[75]
bcl-2 antisense						
+SU 5416	Refractory/relapse	single agent	II	27	0%	Zangari 2004[76]
VEGFR 2 inhibitor						

Abbreviations: EFS: event free survival ; 2 ME 2: 2-methoxyestradiol; ROS: reactive oxygen species; GSH: glutathione (reduced); SAHA: suberoylanalide hydroxyamic acid; VEGFR: vascular endothelial growth factor receptor; na: not applicable; MR: minor response (25%–50% reduction of paraprotein levels).

ing have demonstrated equivalent OS rates, but higher toxicity with Bu/Cy conditioning.[18] Therefore, standard HD-regimens have changed from Bu/Cy to MEL as a single agent or in combination with TBI, IFN and others (Table 2b). In one analysis at our institution, different HD-regimens used in consecutive MM patients receiving an ASCT over a 12.5 year period showed that the median OS of all patients after auto-PBSCT was 59.5 months, which is comparable to earlier studies. Bu/Cy-conditioning seemed to prolong OS in some patients (77.2 vs. 55.6 months), however, this did not reach statistical significance. Since our patient numbers receiving Bu/Cy conditioning were limited, one may speculate that larger numbers might have revealed a small difference. However, earlier analyses have also not observed significant advantages with Bu-conditioning.[17] In addition, side effects are much increased with Bu/Cy so that potential differences in survival seem negligible. Our analysis on the influence of total body irradiation (TBI) on MEL-conditioning revealed no advantage for the combination-therapy (55.6 (+TBI) vs. 59.5 months (-TBI)).[18] This is in line with previous studies, also failing to show any benefit by the addition of TBI (EFS 21 vs. 20.5 months). Moreover, TBI has been reported to cause higher toxicity,[4] thereby potentially deteriorating OS advantages. Therefore, comparable remission and OS rates can be obtained with less toxic conditioning regimens, such as MEL200, thereby significantly reducing side effects. Since this is also an effective treatment option for elderly and frail MM patients, this may, with other diagnostic and therapeutic novelties, further improve treatment outcome in MM.

A randomized trial comparing early vs. late ASCT has shown an improved progression-free survival (PFS) for earlier transplantation (39 vs. 13 months), whereas OS was not significantly different. Earlier transplant was also associated with an improved quality of life and was a favourable prognostic factor.[19] Further studies will determine the benefit of 'upfront' ASCT earlier in the course of disease.

5. 1 vs. 2 vs. more transplants

High-dose chemotherapy with reinfusion of auto- and/or allohaematopoietic stem cells (HSCT) is widely pursued in MM patients and has shown to induce long periods of disease control and to improve long-term OS.[1–4,6] New optimism in MM has evolved due to the refinement of modern therapeutic strategies and treatment success including tandem PBSCT approaches emerging as a promising option for high-risk MM, and seems to be particularly effective for patients with an insufficient response after first-line treatment.[3] Studies comparing tandem vs. single ASCT as summarized in Table 2c have demonstrated improved CR rates by 1–15%, significantly prolonged EFS by 5–12 months and OS benefit in one analysis.[3,20,21]

However, despite treatment intensification partial response or MM relapse is frequent after auto- and allo-

HSCT.[1,19] This seems to result from malignant MM cells, which may have acquired a remarkable ability to survive various conditioning regimens, although previously proven to be chemoradiosensitive. In this context, the origin of MM is still a matter of debate and the malignant cell might be a plasma blast, a plasma cell precursor or the plasma cell itself. Moreover, a transformation from primarily medullary (BM) to secondary extramedullary (EM) MM can evolve spontaneously with time or after HD-therapies.[22] This raises the question, whether transplantation may induce selection of a more aggressive MM cell clone with an altered biology.[22] Preliminary reports provide evidence supporting this hypothesis.[23–25] In one analysis at our centre however, we compared the outcome of 78 MM patients relapsing after auto- (n = 53) or allo- (n = 25) HSCT, stratified into BM (64 patients) vs. EM (14 patients) relapse: the overall (OS) and progression-free (PFS) survival after HSCT in patients relapsing from EM sites was comparable to BM relapse patients, both after auto- and allo-HSCT. Our results suggested that EM relapse may indeed occur both after auto- and allo-transplantation, but that EM relapse may not necessarily induce a worse outcome after transplantation. In conclusion, we found that response to immunotherapy using donor lymphocyte infusions (DLI), either alone or in combination with other anti-MM drugs, was encouraging in patients with active disease after allo-transplantation.[22]

6. Novel agents

Patients not responding well or relapsing after ASCT may benefit from a second ASCT,[3] an allo-HSCT[1] or novel therapeutics. The search for novel molecular targets in MM has given rise to exciting new therapeutic options, including the use of those agents as described in Table 3. These comprise Thalidomide or derivatives (such as Lenalidomide), Bortezomib and others, or combinations of those with standard anti-MM drugs.[26]

Bortezomib is a proteasome inhibitor which has been approved for the treatment of MM patients who received at least one prior therapy and progressed during the last treatment. Within trials it is currently analyzed for upfront-, within conditioning- and maintenance therapies. Bortezomib targets the 26S proteasome, which functions by eliminating cellular proteins tagged for degradation by polyubiquitin chains. Regulated ubiquitin-dependent proteolysis controls cell growth and proliferation, development, apoptosis, signal transduction, gene expression and immune response. Proteins entering the proteasome are stripped of their ubiquitin and degraded through catalytic processes within the core of the proteasome. Bortezomib induces apoptosis in various cancer cells, including MM and other lymphoma cells. It also affects nuclear factor-κB (NF-κB), the bone marrow (BM) microenvironment and various cytokine interactions.[27–29] Bortezomib has been shown to induce an impressive overall response rate of approximately 30% in refractory and relapsed MM patients (SUMMIT-trial). [30] It was tested in the international phase-III APEX-trial which compared Bortezomib vs. Dexamethasone. This study demonstrated that patients on bortezomib achieved a highly significant benefit in time to progression and overall survival (OS).[31] Adverse effects, such as thrombocytopenia, peripheral neuropathy, asthenic conditions, nausea, diarrhoea, anorexia, constipation, pyrexia, vomiting and anaemia were mostly mild, nevertheless, cytopenia and neuropathy should be recognized especially when treating patients over prolonged periods (normally 9–11 weeks) and when using Bortezomib in combination with other cytotoxic drugs.[29] Since Bortezomib is highly effective and preliminary data indicate response rates up to 80% if combined with other agents, it is presently tested within first-line protocols.[32] As its toxicity seems to be limited and stem cell mobilization unaffected, Bortezomib usage within first-line and as part of HD-regimens could further improve the outcome after auto-PBSCT,[23] currently being tested in ongoing clinical trials.

Similarly to Bortezomib that moves fast into first-line therapy concepts, Thalidomide and Lenalidomide are being tested as initial therapy for MM. Phase I studies have determined a significantly more potent and promising preclinical activity, best dosage and schedule and a superior side-effect profile of Lenalidomide than Thalidomide.[33–35] Two large phase III trials have compared Lenalidomide/Dexamethasone to placebo/Dexamethasone in relapsed, refractory MM and preliminary results from both trials show superior response rates and time to progression in favour of Lenalidomide/Dexamethasone.[35] In newly diagnosed MM, one recent phase II trial has used oral Lenalidomide/Dexamethasone as first induction therapy, thereby achieving an overall objective response rate of 91%.[34]

While Bortezomib, Thalidomide and Lenalidomide have already been implemented into large-scale clinical analyses and have been integrated into anti-MM schedules, there are many promising other therapeutic agents in earlier clinical trials (Table 3). These comprise Arsenic trioxide, 2-Methoxyestradiol, vascular endothelial growth factor inhibitor and others which can stabilize the disease in relapse and/or refractory MM. Insight into drug-resistance mechanisms has led to the development of novel agents that sensitize myeloma cells to chemotherapy (bcl-2 antisense). Thus, MM patients have increasingly more therapeutic options. The challenge will be to identify patient subgroups that will benefit most from different agents, and to incorporate targeted therapies into the management, on the basis of an increased understanding of the biology of MM.

7. Relapse therapy

The therapeutic management of relapsed MM patients depends on various factors, including co-morbidities, age and the extent of previous therapies.[36] In case of a planned ASCT, it is usually possible to proceed with stem cell harvesting, even if less than 50% regression has been achieved. If additional cytoreduction is necessary before proceeding to stem cell harvest, options include VAD +/− Cytoxan or other combination therapy protocols, such as DCEP (Dexamethasone, Cytoxan, Etoposide, Platinum), DT-PACE (Dexamethasone, Thalidomide, Platinum, Adriamycin, Cytoxan, Etoposide), IEV and CEV. Dexamethasone alone is also effective. When the patient does not qualify for stem cell harvesting and transplant, Melphalan as a single agent or as part of a combined regimen, such as ABCM (Doxorubicin, BCNU, Cyclophosphamide, Melphalan) or VBMCP (Vincristine, BCNU, Melphalan, Cyclophosphamide, Prednisone) can be consid-

ered. Further, novel therapeutic agents, such as Thalidomide, Lenalidomide, Bortezomib or those described in Table 3, will become an integral part of good patient care. These may prove to be increasingly effective in the combination with standard anti-MM drugs, such as anthracyclines and alkylating agents. Preliminary results of combining Thalidomide, Bortezomib and Dexamethasone for relapsed/refractory myeloma have also been attained, which albeit its need to be confirmed by others and a longer observation period, are very encouraging and possibly a well tolerated regimen in MM patients.[37]

8. Maintenance therapy

The role of anti-myeloma maintenance therapy is increasingly important, since with patients achieving a good response following frontline therapy and/or stem cell transplantation, this is aimed to be preserved. For an effective implementation of a maintenance approach, objective criteria need to be defined for its initiation, since it is not as yet clear whether it should be initiated in all patients or especially in high-risk patients.

Maintenance with alpha-Interferon has proven to provide only a marginal benefit. Although remission duration was prolonged by 4–7 months in some studies, no benefit for OS has been shown so far.[38,39] However, since some of these trials had relatively small study cohorts, the results of large ongoing intergroup trials in the USA and Europe have to be awaited.

Steroids are the simplest agents for maintenance therapy. Low-dose prednisone (50 mg every other day) has shown favourable PFS and OS rates in patients who achieved a response to induction chemotherapy.[40] Although this is a very promising approach and has surely found its way into clinical practise, further studies of benefits, side effects and quality of life are required.

Promising strategies also comprise the single agent use or combination regimens of Thalidomide, Lenalidomide, Bortezomib and others. Thalidomide maintenance after double ASCT increased PFS in a first analysis 40 months after treatment initiation from 53% to 70%.[41] Although a definite benefit for OS could not be proven so far, these results suggest Thalidomide as an effective option which is currently pursued further. In conjunction with these promising advances, specific maintenance therapy must be assessed in the individual patient, based upon the level of residual disease and the anticipated potential for renewed disease activity.

9. Supportives

Despite substantial innovations in the antineoplastic treatment of MM, specific supportive therapies have conferred a key role in patient management and largely contribute to high-standard patient care.

Approximately 80% of MM patients have lytic bone lesions and/or diffuse osteopenia. Bisphosphonates, which substantially inhibit new bone destruction, are recommended for all MM patients with bone disease. International standard is the use of intravenous zoledronic acid or pamidronate every four weeks in stage II and III disease. According to the ASCO guidelines, the use of biochemical markers of bone metabolism to monitor bisphosphonate use is not recommended.[42] In addition, bisphosphonates have a beneficial impact on pain control, in particular with pain due to osteolytic disease. As a recently reported rare complication, Bisphosphonate-associated osteonecrosis of the mandible and maxilla in cancer patients may occur.[43–48] The risk factors and precise pathogenetic mechanisms involved are not known so far. Several multimodal therapeutic approaches did not prove to be effective, including discontinuation of bisphosphonates, surgical intervention, antibiotic therapy, hyperbaric oxygen therapy, and topical use of chemotherapeutic mouth rinses,[49] but need to be studied further to define patients at risk.

Approximately 70% of MM patients have a degree of anaemia resulting from cancer or its therapy that can be treated with the recombinant haematopoietic growth factor erythropoietin. Evidence-based guidelines recommend erythropoietin, when haemoglobin levels fall below 10 g/dL and for patients with persistent symptomatic anaemia. Good evidence from clinical trials supports the use of subcutaneous erythropoietin weekly, twice or three times weekly. Erythropoietin should be titrated once the haemoglobin concentration reaches 12 g/dL.[50]

Infection is the most dangerous complication for MM patients, since disease and therapy impair both cell-mediated and humoral immunity. Patients are susceptible to viruses, bacteria, mycobacteria, fungi and other pathogens and require a thorough infection monitoring, prophylaxis and aggressive treatment. In addition, all allo-transplanted patients should receive vaccinations for Diphtheria, Tetanus, *Haemophilus influenzae* type b, Influenzavirus, Poliovirus, Measles, Mumps, Rubella and *Streptococcus pneumoniae*, while for auto-transplanted patients, most importantly, vaccinations for Influenzavirus and *Streptococcus pneumoniae* are recommended.[10,51]

10. Secondary MM

Despite significant improvement in cancer prognosis due to novel CTx combinations, targeted therapies and intensive strategies, treatment-related complications, the most serious being secondary malignancies, may occur. These secondary malignancies mostly comprise of acute leukaemias, especially acute myeloid leukaemias (AML) and myelodysplastic syndromes (MDS), but also solid tumours (ST) and Non-Hodgkin's Lymphomas (NHL).[52,53] Genetic predisposition to malignant tumours and impaired immunosurveillance due to the first malignancy and therapy-related immunosuppression may present key factors for secondary tumours, including MM to evolve years after the initial tumour diagnosis and treatment. The history of alkylating CTx and extended radiotherapy may also promote secondary malignancies.[53] Additional risk factors may be young age at diagnosis of the first tumour and splenectomy. Furthermore, since the BM has exhibited a higher radiosensitivity than other organs, and extended radiation involves considerable BM areas, this might in part explain the formation of secondary tumours at this site. There are several studies on the overall incidence of secondary NHLs following primary tumours. As the various NHL subtypes have not been clearly distinguished in previous analyses, it could be speculated that a number of MM might be concealed within these data.[53]

To further estimate treatment-related secondary malignancies, especially low-grade NHL (including MM), it is desirable to collect epidemiological data on the general population and cancer survivors. Further, comparison of different treatment protocols and assessment of individual risks for secondary cancers are needed for the development of less carcinogenic treatment protocols. Moreover, lifelong follow-up of cancer survivors is an indispensable objective. Since the prognosis of secondary malignancies, especially leukaemia and MDS, is often dismal, early detection, risk stratified chemotherapy-regimens and less radiotherapy will help to decrease secondary cancers in the future.[53]

11. Conclusion and perspectives

Modern treatment concepts, comprising ASCT, provide a safe and highly effective therapy with which a substantial proportion of MM patients survive for more than ten years. Although residual disease may be detectable with molecular methods, we are aiming at normal life for MM patients, without symptoms relating to the disease or its complications. A most promising therapeutic option yet may be the combination of transplantation procedures and targeted therapies. An increasing understanding of the disease biology means a largely broadened spectrum of targeted therapies that allows and obliges us to further ameliorate outcome and quality of life. For example the tumour suppressor involved in the pathogenesis of the disease in high risk patients (e.g. deletion 13q14) is still uncertain. Exciting progress has introduced a new concept in cancerogenesis which has drawn broad attention. A class of recently discovered small non-coding RNA (microRNAs or miRNAs) can negatively regulate gene expression and seem to be involved in the development of several cancers and may act as both tumour suppressor and oncogene.[54] Several of the miRNA genes are located on chromosome 13 and two of them in the region 13q14, thus making them a promising tumour suppressor with a role in MM pathogenesis. These new basic discoveries about gene regulation in tumourigenesis are likely to lead to the development of new treatment options. Despite impressive advances in MM therapy, there are still important challenges to overcome in the future. In addition to targeted therapies chemotherapeutic regimens with an increased antineoplastic efficiency are needed, since the major cause of relapse even after high-dose chemotherapy is biological resistance of the tumour to cytotoxic agents. This is a very exciting time in the field MM, and we are eager to see further advances in the years ahead.

Conflict of interest statement

None declared.

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