The evolving treatment paradigm of multiple myeloma: From past to present and future

Sürekli gelişmekte olan bir tedavi yaklaşımı: Multipl miyeloma tedavisinin geçmişi, bugünü ve geleceği

Meral Beksaç, Michel Delforge[1], Paul Richardson[2]
Ankara University, Medical School, Hematology Department, Ankara, Turkey
[1]University Hospital Gasthuisberg, Department of Hematology, Leuven, Belgium
[2]Jerome Lipper Myeloma Center, Division of Hematologic Oncology, Dana Farber Cancer Institute, Harvard Medical School, Boston, USA

Abstract
Multiple myeloma has been recognized since at least the middle of the 19 th century. The list of therapies used in the treatment of myeloma is long but only recently has therapeutic success approached a level commensurate with disease control, although cure remains elusive. The complexity of the disease, invidual variations and very active ongoing clinical research warrants continous updating of current information. This review not only summarizes the level of success that has been achieved during the past years but also points to the drawbacks in the current treatment strategies giving emphasize to the potential solutions in the future. *(Turk J Hematol 2008; 25: 60-70)*
Key words: Multiple myeloma, treatment, review

Özet
Multipl Miyeloma bilindiği kadarıyla 19.Yüzyılın ortalarından beri tanınan bir hastalıktır. Tedavi yöntemleri listesinin çok uzun olmasına rağmen, tedavi başarısı ancak son zamanlarda hastalığı kontrol altına alabilecek düzeye ulaşabilmiştir. Şifa konusu ise hala belirsizlik taşımaktadır. Hastalığın karmaşık yapısı, kişisel farklılıklar ve bu alanda süregelen klinik araştırmaların varlığı, bilgilerin devamlı güncellenmesini gerektirmektedir. Bu derleme bugüne kadar ulaşılan başarı düzeyini, tedavideki sorunları özetlerken gelecekte bunların çözümlerine yönelik olasılıkları da içermektedir. *(Turk J Hematol 2008; 25: 60-70)*
Anahtar kelimeler: Multipl miyeloma, tedavi, derleme

The Past

Multiple myeloma has been recognized since at least the middle of the 19 th century. The list of therapies used in the treatment of myeloma is long but only recently has therapeutic success approached a level commensurate with disease control, although cure remains elusive. About 150 years ago, when myeloma was initially described by Dr. Henry Bence-Jones in London, patients were being treated with Dower's powder, camphor, julep, ammonium acetate, cupping, blood removal, leeches, steel and quinine. One hundred years later, urethane and stilbamidine were added to the list by Nils Alwall from the University of Lund. A randomized trial tested urethane against placebo and no benefit was seen. Melphalan was not used until 1958 when Blokhin (USSR) described remarkable activity with its use, and in 1962 Bergsagel (MD Anderson) reported the best results [1]. Since then, Melphalan with glucocorticoid has been a standard combination in myeloma. Indeed, the Oxford myeloma trialists group conduc-

Address for Correspondence: Dr. Meral Beksaç, Ankara University, Medical School, Hematology Department, Ankara, Turkey
Tel: +90 312 595 73 45 E-mail: beksac@medicine.ankara.edu.tr

ted a meta analysis (incorporating 35 years of expertise and 20 trials involving 4930 patients) which revealed superior responses (60% vs 53.2%, p<0.00001) but a statistically insignificant reduction in death rate (1.5%) and no impact on survival with combination therapies compared to melphalan +prednisolone (MP). Since melphalan is toxic to hematopoietic stem cells and mobilisation, combination chemotherapies including VAD (vincristine, adriamycin,dexamethasone), VBMCP (vincristine, BCNU, melphalan, cyclophosphamide, prednisone), VBAP/(vincristine, BCNU, Adriamycin, predisolone /dexamethasone), ABCM (Adriamycin, BCNU,Cyclophosphamide, methotrexate) have been favored prior to transplant. A comparison of ABCM vs Melphalan alone, reported by MRC and not included in the meta analysis, showed a benefit with ABCM, but when this outcome was compared with MP in the meta analysis the advantage dissappeared. Therefore it is generally accepted that the combination therapies and MP were in fact roughly equivalent [2-5].

Melphalan is hydrolysed and excreted via the kidneys but the extent of drug accumulation is variable in each individual and cannot be predicted from the degree of renal impairment. Manufacturers' data recommend that initial doses of melphalan should be reduced by 50% if the glomerular filtration rate (GFR) is <40–50 ml/min and titrated against bone marrow toxicity in subsequent courses. Another widely used regimen has been intravenous (IV) VAD, which was first described by Alexanian in 1992. It gained popularity by lacking stem cell toxicity and nephrotoxicity; VAD and MP have never been tested in the same trial and carry many differences including iv vs oral, high dose vs standard dose steroids, and differing toxicity profiles. The major advantage of VAD came from high dose dexamethasone, as Vincristine alone is not active against myeloma and adriamycin's activity is modest when combined with dexamethasone [3,4].

The Present:

I. Evaluation of response to therapy

Evaluation of response has recently been re-defined by the scientific advisory board members of the International Myeloma Foundation and the term "uniform criteria" has been coined [6]. As originally defined by the European Blood and Marrow Transplant group (EBMT) and accepted by International Bone Marrow Transplant Registry (IBMTR) as well as other agencies (including the US FDA and EMEA), evaluation of tumour response is based on changes in serum levels of M-protein and/or urinary light chain excretion as well as bone marrow involvelment and bone disease [7]. The new international uniform response criteria (IURC) builds on the EBMT criteria and implements the use of free light chains, especially in the context of nonsecretory myelomas. IURC also seek to define response more rigorously with a new criteria of stringent complete response (sCR), which includes the disappearance of clonal plasma cells demonstrated by flow cytometry, immunocytochemistry or molecular methods. Very good partial response (VGPR), has been incorporated and CR is possible only with disappearance of clonal proteins by immunofixation, with the new criteria not requiring a minimum six week period for evaluation of response. Recommendations for intervals in M-component measurement suggest monthly for a year followed by bimonthly thereafter, and progressive disease (PD) now requires more features than simply immunofixation positivity (from CR) or less clinically relevant increases in M protein. It is anticipated that upcoming clinical trials will provide us an opportunity to compare the EBMT criteria and these new criteria, validating their use and hopefully improving our ability to measure clinical benefit accordingly.

II. Standard dose combination therapies

During recent years, there have been many publications comparing combination chemotherapies with autologous transplants (ASCT). In these studies MP (GIMMO), VAD (MAG), VMCP/VBAP (IFM, SWOG), C-VAMP (MRC), VBMCP/VBAD (PETHEMA) therapies have been compared to ASCT. Three of these trials showed improved survival with ASCT [8-12] and provides the basis for ASCT as a standard of care in younger patients with myeloma. However, two trials using the same combination treatment (VBMCP) as standard dose found no benefit from ASCT on overall survival [11-12]. One of these is the PETHEMA trial where only responding patients were randomized [12]. The complete remission (CR) rate was significantly higher with ASCT (30% vs 11%; P=.002). However, progression-free survival (PFS) was not significantly different between ASCT and standard dose therapy (SDT) (median, 42 vs 33 months), and overall survival (OS) was similar in both groups (median, 61 vs 66 months). In the SWOG S9321 trial, all patients following an initial combination of VAD were randomized to ASCT or SDT [11]. Extended courses of VMCP up to 12 months increased the CR rate from 5 % (after four courses of VAD) to 15 %. Remarkably, ASCT and SDT yielded comparable response rates, as well as PFS and OS durations (PFS: 17% and 16%, OS: 37% and 42%, respectively). The CR rate following ASCT was 17%, a result less than that obtained in most other ASCT trials. Conversely, the CR in the control arm was better than most of the previous trials which may in part be explained with the duration and composition of the VBMCP combination. Interestingly, with VBMCP/VBAP as frontline therapy, the PETHEMA had obtained a CR of 11%. It is noteworthy that there has never been a prospective comparison of VAD vs VMCP vs VAMP vs C-VAMP. With these regimens CR ranges between 10-25 %. The disadvantages include risk of catheter infection (30-35%) and thrombosis (5-8%), in addition to cardiotoxicity, neuropathy, mucositis and alopecia.

III. Initial therapy and treatment prior to high dose therapy (ASCT)

Key questions when considering treatment initiation include when to start, with what combination, for how long and which patients are candidates for intensive treatment. The generally accepted approach is to observe carefully and delay treatment in smoldering (asymptomatic) myeloma until signs of disease progression and end organ involvement such as anemia, hypercalcemia, bone lesions and renal dysfunction. Careful, frequent follow up with sensitive tools including SPEP, immunofixation(IF), FLC (Free Light Chain) and appropriate radiology testing such as plain films, PET/CT and MRI as clinically indicated, during this early phase are important. Once the decision to treat is made, the question arises about candidacy for ASCT and eligibility for a clinical trial. Advanced age and/or significant co-morbidity are important limitations for ASCT. Moreover, for ASCT candidates, it is important to avoid melphalan prior to ASCT [1,3,5,7].

Oral combinations incorporating novel agents have been designed to overcome intravenous line related complications and improve response rates. These include Thalidomide-Dexametha-

sone (TD), Idarubicin-Dexamethasone (Z-Dex), and Cyclophosphamide-Thalidomide-Dexamethasone (CTD) [5,13-19]. Rapid infusion VAD has also been shown to be as effective as VAD in newly diagnosed patients by HOVON [7]. Z-Dex has been found to be an effective regimen but the overall response rate (RR) is not significantly superior to VAD at 58% vs 74% (p=0.075) [5,7]. Since high dose Dex (HDD) is considered the most potent component of VAD regimen, it has been used as a single agent and found to induce 62 % reponse rate, similar to the overall response obtained with VAD(74%, p=0.25) when given before ASCT [7]. HDD alone has been widely used in the USA for initial therapy prior to ASCT, but now has been supplanted by newer regimens.

Specifically, TD has now been compared with Dex alone prospectively or with VAD both retrospectively and prospectively [13-20]. All reports to date have demonstrated the superiority of TD. A key prospective study compared TD vs high dose Dex with a response rate of 63% vs 41% (p<0.002). In a retrospective analysis Cavo et al have reported: TD vs VAD (CR: 76% vs 52%, p<0.001 [14]. In a similar retrospective evaluation, the same group reported on an intent-to-treat basis, stringently defined (immunofixation negative) complete remission (CR) rate following double ASCT and TD of 54% [16]. This value was significantly higher (P=0.0009) compared to the 33% observed in a comparable series of 129 pts who received double ASCT without TD. In comparison, addition of TD to double ASCT significantly prolonged PFS (median: 31 vs 42 months; P=0.04) and did not adversely affect survival after post-transplant relapse (P=0.7). In a prospective study, the MAF group reported an initial benefit of TD vs VAD (before stem cell collection:VGPR:25% vs 7%(p=.0027) before ASCT: 35% vs 13%(p=.002)). 6 months post single ASCT, with equivalent response rates seen at : 44% vs 42% [15]. Another frontline combined treatment approach with Thalidomide is the TAD regimen administered in the HOVON/ 50/GMMG-HD3-Trial [19]. TAD % induced a significantly higher response rate both before (49% vs. 32%, p<0.001) and following (72% vs. 54%, p<0.001) ASCT. Whilst CR rates proceeding ASCT in the French and German/HOVON trials are in accordance with the Italian results, post ASCT response rates did not show an survival advantage (76% and 79%) in favour of TD or TAD (HOVON data: TAD vs VAD (XI.IMMW2007, EHA 2007) UKMMIX (CTD vs CVAD (XI.IMMW 2007) [20]. Similarly, in the IFM 2005-01 trial, VD was advantageous compared to VAD in terms of both pre and post ASCT response rates (XI.IMMW 2007) [21].

It is important to note that the increased response rate with thalidomide-based regimens is balanced with an increased risk of venus thrombosis (DVT) and neuropathy. Interestingly, DVT risk (at 15-17%, without thrombo-prophylaxis) is more frequent during the first 3 months of treatment, increases with age and warrants prophylactic anticoagulation with either LMWH, therapeutic coumadin or full dose aspirin. Nevertheless, this oral combination does not require hospitalization and does not compromise successful harvest of stem cells. There is cumulating evidence that better RR achieved with TD improves outcome, although in some settings (specifically total therapy) there are doubts about its impact on post-transplant relapse and OS. The use of this combination in elderly patients also warrants caution and some authors have suggested initiating treatment in patients with low tumor burden with Dex alone and assessing the response within 1-2 months, and adding thalidomide if required [13,18]. Conversely, the combination is recommended for patients with advanced disease and/or those with poor prognostic features [13,18]. Moreover, thalidomide at low dose may be effective in the management of patients with renal failure, but caution is needed in patients with serious renal or hepatic failure and there is limited published data. The clearance of thalidomide is increased during dialysis; but it does not appear necessary to give a supplementary dose. Indeed, 1% of thalidomide is excreted unchanged in the urine and it does not appear to be hepatically or renally metabolised to any large extent, appearing to undergo non-enzymatic hydrolysis in plasma to form multiple degradation products, so that it is reasonable to utilize this agent as part of a combinationin this setting [5].

The impact of thalidomide as part of induction and maintenance in an intensive treatment protocol has been evaluated in a recent publication by Barlogie [19]. Patients were randomized to thalidomide (+) vs no thalidomide during primary remission-induction therapy, between two ASCT, with consolidation therapy, and as maintenance treatment. The thalidomide treated patients had a significantly higher rates of both CR (62 % vs. 43 %) and five-year EFS (56 % vs. 44 %). However, OS curves in the two groups were similar in part due to the poorer outcome after relapse in the thalidomide group. In particular, thalidomide-treated patients had a lower rate of response to salvage therapy and shorter OS after relapse than the control patients. Most debilitating was the incidence of peripheral neuropathy (grade of 2 or grader) which was more common in the thalidomide group than in the control group (27 % vs. 17 %, P<0.001) and among patients at least 65 years old than among younger patients (29 % vs. 20 %, P=0.02). Peripheral neuropathy improved to less than grade 2 within three to four months after a dose reduction or cessation of thalidomide in most patients. Severe constipation, neutropenia were also more common in the thalidomide group. Treatment after relapse included further thalidomide or thalidomide (75 % of the thalidomide group and 83 % of the control group), other agents and further high-dose therapy (7 % and 2 %, respectively). Although survival after relapse was longer (2.7 vs. 1.1 years, P=0.001) among patients initially assigned to receive no thalidomide than among those assigned to receive thalidomide, it is important to note that the majority of the control group received thalidomide following relapse. Based on these findings, the impact of CR on survival and the higher rate of failure to respond to salvage therapy in the thalidomide-treated group warrants caution, especially with respect to the salvage potential of thalidomide-containing regimens in patients who had received thalidomide throughout their treatment. The study authors draw attention to bortezomib as second-line therapy for myeloma: response rates to bortezomib are superior regardless of the type of first-line therapy, with the exception of prior thalidomide treatment and thus have speculated on the implications of thalidomide resistance in this setting for being an especially poor prognostic feature. This requires further study but other trials have not supported this finding [22].

Whilst a meta analysis on four SWOG Phase III trials revealed no impact of response to frontline therapy on OS and PFS [23], there are numerous reports showing achieving CR (after HDT as well as CR not completed by ASCT) appears to be a good prognostic factor for remission duration and overall survival (OS) [5,23-24], The ECOG E 9486 study showed the prognostic role of CR obtained by combination therapy alone (VBMCP+/-INF) [24]. The median duration of survival from the date of objective response was 5.1 years for those who achieved a CR and 3.3 years for those with a partial response (P<.0001). The median post response survival was 6.6 years in the 21 patients in CR with no marrow disease, and 4.4 years in the 11 patients in CR who had persistent marrow disease.

A key novel agent, bortezomib has been used in newly diagnosed patients prior to ASCT. The SUMMIT investigators reported a response rate of 40%, with 10% CR (which is similar to that previously reported in refractory patients) when used as monotherapy in 66 patients. Dispenzieri et al., using the same dose and schedule in a smaller study of higher risk patients observed an encouraging response rate (≥PR 73%) [22,25]. These differences may be due to the number of cycles administered (median 3 vs 5, respectively). The addition of dexamethasone improves response rate (≥PR 80-90%, with 18% CR or near CR) [26]. Recently the IFM group have presented their preliminary findings comparing bortezomib and dexamethasone versus VAD, consolidated with DCEP preceeding ASCT [27], which have been very encouraging. Similar results were obtained with the PAD regimen (bortezomib, adriamycin, and dexamethasone) (89% response rate, with 16% CR or near CR) and the VTD scheme (bortezomib, thalidomide and dexamethasone) (92% RR with 19% CR) [27,28]. These results suggest that the majority of newly diagnosed MM patients will respond to bortezomib-based regimens and around one in five will achieve CR, resulting in a picture similar to that observed after ASCT. Moreover, all these studies showed that stem cell mobilization was not hampered with prior Bortezomib therapy. Importantly, the use of high dose melphlan after these bortezomib-based induction regimens was associated with an impressive improvement in the CR rate. Thus, in the PAD study, the 16% CR or near CR prior to ASCT increased to 54% after melphlan at 200mg/m^2; in the DT-PACE study the percentage of CR increased from 16% to 58%, and in the VTD from 19% to 31%. These data strongly support the complementary value of this sequential strategy (i.e., novel drugs combinations upfront, followed by ASCT) [29].

In a large phase II study conducted by the IFM, Bortezomib and Dex combination was evaluated [26] and an overall RR of 66% was repeated, including 21% CR and 10% very good partial remission (>90% reduction of the M-component). Side effects were mild to moderate, and manageable. Peripheral neuropathy was observed in 15 cases but was grade 2-3 in only seven cases (14%). There was no DVT and no hematologic toxicity greater than grade 2. Grade 3 infections were recorded in 5 patients, including 3 who had herpes zoster infections, readily treated with anti-viral treatment and subsequently prevented with acyclovir prophlaxis. Stem cell collection was planned in 44 patients and all had sufficient CD34+ cells to perform at least one ASCT (> 2x10^6/kg).

Another key novel agent lenalidomide has been combined with high dose dexamethasone in the upfront study. Remarkably high response rates were seen, with thirty-one of 34 patients achieving an objective response, including 2 (6%) achieving complete response (CR) and 11 (32%) meeting criteria for both very good partial response and near complete response, resulting in an overall objective response rate of 91% [30]. This drug has recently received approval from FDA for use in relapsed patients and should be commercially available in Europe soon, as EMEA approval was granted in March 2007.

As can be seen from these results the landscape of myeloma treatment has changed substantially over the past few years. New agents have moved rapidly from the bench to the bedside and they are now important additions to the treatments available for the initial treatment of myeloma. Currently, the main clinical challenges are optimizing the use of these new agents: specifically, should they be given sequentially or in combination, and how they should be integrated with conventional therapies? One strategy is to eradicate the tumor with the use of a combination of all, or most of, the available agents and continue to utilize double ASCT. Whether such an approach can modify the course of myeloma is uncertain, as reflected in the study by Barlogie [19]. About 15 % of myeloma patients are aged <60, with an additional 15% aged 60-65, and only 2% are <40 . Whilst the overall RR with total therapy is impressive (80%), there is a cost for a 50% CR rate: considerable toxicity, treatment-related mortality (5%) and the use of intensive treatment, which compromises quality of life. Another approach is to use new agents for the sequential treatment of disease as a means of controlling the growth or regrowth of tumor, thereby converting myeloma into an indolent disease with durable remission as a primary goal and quality of life a key consideration. Ongoing studies using novel agents before, during, and following post ASCT or as part of maintenance will hopefully help answer this question.

Moreover, genomic and proteomic studies incorporated into new trials identify molecular mechanisms of drug sensitivity and resistance, and potentially aid in the design of treatment for individual patients. It is important to note that the overall message is one of great hope. Through biologic and clinical research in myeloma, we are providing effective new treatments that promise long-term benefit to a substantial proportion of patients with a cancer for which only short term palliation was a goal, even as recently as a decade ago [31].

IV. Initial therapy where ASCT is not planned

Standard first-line treatment for multiple myeloma (MM) patients ineligible for ASCT has been MP, with only rare CRs seen. The aim of therapy in these patients (usually older and less fit) is to achieve a response with minimal treatment-related toxicity. Thus either melphalan or cyclophosphamide with or without prednisolone have been used. Doses are modified according to nadir cell counts, bearing in mind that antimyeloma activity is usually achievable with doses that cause some degree of myelosuppression. Cyclophosphamide causes less cytopenia and is recommended for patients with neutrophil counts below 1·0x10^9/l or platelet counts below 75x10^9/l. Duration of therapy is guided by the principle of achieving maximum res-

ponse and then course of treatment for an additional 3 months, as several randomized trials have shown no advantage of continuing chemotherapy further [1-5].

The IFM group randomized 488 newly diagnosed patients aged 65 to 75 years, between 4 regimens of treatment: namely, melphalan-prednisone, dexamethasone alone, melphalan-dexamethasone, and dexamethasone-interferon alpha. Response rates at 6 months (except for complete response) were significantly higher among patients receiving melphalan-dexamethasone, and PFS was significantly better among patients receiving melphalan (P < .001, for both comparisons), but there was no difference in OS between the 4 treatment groups. Moreover, the morbidity associated with dexamethasone-based regimens was significantly higher than with MP, especially for severe pyogenic infections in the MD arm and hemorrhage, severe diabetes, and gastrointestinal and psychiatric complications in all the dex -containing arms. Overall, these results indicated that dexamethasone should not be routinely recommended as first-line treatment in elderly patients with MM. In the context of the IFM 95-01 trial, the standard MP remained the best treatment choice when efficacy and toxicity were both considered. However, the CR rate remained disappointingly low at only 1-3 % in all arms [32].

The benefits observed with novel agents ie thalidomide, bortezomib, revlimid in refractory or relapsing patients have prompted clinicians to integrate these agents into the MP protocols. The comparative effectiveness and toxicities of these novel agents are summarized in Table 1 and 2.

The exciting benefits of thalidomide in combination with MP compared to MP alone have been published by Palumbo [33]. Patients treated with thalidomide had higher response rates and longer EFS than patients who were not. Combined CR or PR rates were 76% for MPT and 48% for MP alone, and the near-CR or CR rates were 28% and 7%, respectively. Two year EFS rates were 54% for MPT and 27% for MP (hazard ratio [HR] for MPT 0·51, p=0·0006), with 3 year survival rates of 80% for MPT and 64% for MP (HR for MPT 0·68, p=0·19). However, rates of grade 3 or 4 adverse events were 48% in MPT patients and 25% in MP patients (p=0·0002). Introduction of enoxaparin prophylaxis reduced the rate of thromboembolism from 20% to 3% (p=0·005).

Similar but larger, three armed French study (IFM 99-06) compared MP vs MPT vs ASCT, a key question in this older population, where transplant may be significantly more toxic [34]. They observed median PFS times of 17.1, 27.6 and 19.0 months in MP, MP-T and MEL100 groups, respectively. The PFS time was significantly longer in the MP-T group than in the MP group (hazard ratio estimate, RR=2.4, 95% CI=1.8–3.3, P<0.0001). The PFS advantage in favor of MP-T group translated to a significant benefit in terms of OS. Median OS times were 30.3 months (86 deaths), not reached at 55 months (34 deaths) and 38.6 months (52 deaths) in MP, MP-T and MEL100 groups, respectively. The OS time was significantly longer in MP-T group than in MP group (RR=1.9, 95% CI=1.3–2.9, P=0.0009). In the secondary OS comparison, superiority of MP-T on MEL100 was evident (RR=1.7, P=0.022). Since these results unequivocally show the superiority of MP-T, enrollment was stopped after this analysis. The survival ad-

Table 1. MP containing regimens: Comparison of Efficacy

	Melphalan+ Prednisone+ Thalidomide MPT	Melphalan+ Prednisone+ Thalidomide MPT	Melphalan+ Prednisone+ Bortezomib MPV	Melphalan+ Prednisone+ Lenalidomide MP-R	Thalidomide +Dexamethasone TD	Thalidomide +Dexamethasone (low dose) TD
n	124	129	60	50	84	50
CR	16%	16%	32%	24 %	8%	34%
authors	Facon et al.[34]	Palumbo et al.[33]	Mateos et al.[35]	Palumbo et al.[41]	Ludwig*	Offidani et al.[36]

*: ASH 2006 abstract

Table 2. New drugs in MM: Most common side effects

	thalidomide	lenalidomide	bortezomib
Hematological			
myelosuppression	rare	anemia,neutropenia, thrombocytopenia	thrombocytopenia
Non-Hematological			
gastro-intestinal	constipation	constipation, diarrhoea	constipation, diarrhoea
polyneuropathy	++	-	+
thrombogenicity	in combination	in combination	-
fatigue	+	+	+
teratogenicity	+	?	-
skin reactions	+	+	+

vantage observed in the French study has not yet been seen in the Italian study, although follow-up is still early. Moreover, it is important to draw attention to the differences in the treatment durations and the age limits between the trials [33-34]. There are ongoing trials currently active in the Nordic countries, other part of Europe and Turkey comparing MP with MPT, with a meta analysis planned in the near future.

To potentiate the response in elderly, newly diagnosed myeloma patients, bortezomib has been added to the MP protocol. A phase 1/2 trial in 60 untreated MM patients aged at least 65 years (with half older than 75 years) was carried out to determine dosing, safety, and efficacy of bortezomib plus MP (V-MP) [35]. Remarkably, the V-MP response rate was 89%, including 32% immunofixation-negative CRs, of whom half of the IF- CR patients analyzed achieved immunophenotypic remission (with no detectable plasma cells at 10-4 to 10-5 sensitivity). In addition, V-MP appeared to overcome the poor prognosis conferred by retinoblastoma gene deletion and IgH translocations in this patient population. These results compare favorably with historical control data for MP, most notably, in response rate (89% versus 42%), EFS at 16 months (83% versus 51%), and survival at 16 months (90% versus 62%) which were all significantly superior. Side effects were predictable and generally manageable. Principal toxicities included hematologic, gastrointestinal, and neuropathic side effects were more evident during early cycles and in patients aged 75 years or more. In conclusion, in elderly patients and/or those ineligible for ASCT, the combination of bortezomib plus MP appeared to be significantly superior to MP, producing very high CR rates, and immunophenotypic CRs, even in patients with poor prognostic features. Based on these findings a multicenter trial (VISTA) comparing MP vs VMP has been inititated and was recently completed [29].

Efforts to improve ASCT in older patients have included a study by Palumbo that evaluated a group of patients who were not candidates for standard dose of 140-200 mg/m^2. [10] Melphalan was given in two courses of 100 mg/m^2. Melphalan with stem cell rescue was compared to a control group who received MP alone. Near CR was achieved in just 6% after MP and 25% after MEL100 (P =.0002). At 3 years, MEL100 increased EFS from 16% to 37% and OS from 62% to 77% (P < .001). Similar results were observed in patients aged 65 to 70: near CR was 8% after MP and 25% after MEL100 (P=.05); at 3 years, MEL100 improved EFS from 18% to 31% (P=.01) and OS from 58% to 73% (P=.01). Patients aged 65 to 70 had a median OS of 37.2 months (MP) versus 58 months (MEL100). Intermediate-dose melphalan thus improved response rate, EFS, and OS in older myeloma patients, specifically in those aged 65 to 70. This provided the basis for the ASCT arm in the French study discussed previously, and suggests ASCT may still be an option for selected patients [10-11, 34].

As described above, the address the role of ASCT and addition of thalidomide, the prospective French study (IFM 99-06) was designed not only to compare MP vs MP-T but to evaluate in this population ASCT as well [34]. Remarkably, the study showed a benefit from MPT vs ASCT, although CR rates following MPT vs Mel100, were 15% vs 17%. EFS and OS were significantly better with MPT at 29.5 vs 19 months and >55 vs 38.6 months, suggest that ASCT should be utilized, if at all with care.

Similarly, a recent published report has evaluated the role of thalidomide-dexamethasone-liposomal doxorubicin (ThaDD) in untreated patients older than 65 years. Offidani and colleagues reported that ThaDD yielded 36-month EFS and OS rates of 57% and 74%, respectively. Toxicities were manageable, with response rates of 34% CR, 7% nCR, and an ORR of 98%. Three year projected TTP, EFS and OS were all significantly higher in those patients achieving a response of at least VGPR, versus those who did not. These are comparable with ASCT, but long term OS and EFS remain to be seen [36].

The Arkansas group have drawn attention to myeloma which evolves from MGUS and has a lower CR rate but without any apparent adverse consequences on survival. Also, within their experience, despite similar CR rates of 40% after high dose melphalan treatment, one third of patients with cytogenetic abnormalities have a short median survival of only 2 to 3 years, compared with 7 or more years in the remainder. Thus, although high CR rates in the setting of ASCT may translate into extended survival for patients with standard-risk myeloma, this may not hold true following treatment with the newer non-genotoxic agents and ongoing studies will be key in resolving this issue [60].

Barlogie et al have published an analysis on prognostic factors in thalidomide-treated patients [37]. They describe thalidomide dose escalation (200 mg/d; 200 mg increment every 2 weeks to 800 mg) for 169 patients with advanced myeloma (abnormal cytogenetics: 67%; prior autotransplant: 76%) extending their earlier results reported in 84 patients [38]. A 25% myeloma protein reduction was obtained in 37% of patients, with a 50% reduction in 30% of patients and a near-CR or CR in 14%. Responses were in patients more frequent with low plasma cell labeling index (PCLI) (below 0.5%) and normal cytogenetics. Two-year EFS and OS rates were 20% and 48% respectively, and again were superior with normal cytogenetics, PCLI of less than 0.5%, and 2-microglobulin of 3 mg/L or less. Conversely, response rates were higher and survival was longer in high-risk patients given more than 42 g thalidomide in 3 months as a median cumulative dose. This suggests a need for high doses of thalidomide in higher risk myeloma but this is an area of controversy as lower doses appear to be better tolerated [37].

In contrast, bortezomib appears to be highly active irrespective of higher risk features: specifically, in a subgroup of patients in the APEX study were analyzed for presence of cytogenetic abnormalities and bortezomib was found to be active regardless of 13 q deletion [22,39]. Moreover, a recent publication [40] about Bortezomib treated 65 patients have revealed superior clinical response with or without 13q deletion (77% versus 50%); t (4;14) (67% versus 56%); t (11;4) (33% versus 62%), or CKS1B amplification (67% versus 57%). Similar observations are also being reported now with lenalidomide [41].

V. Patients relapsing or refractory to initial therapy

There is a lack of evidence from randomised controlled trials on the optimal approach to treating primary refractory disease. However, it is clear that patients refractory to one regimen may respond well to another regimen in this setting. For example, patients refractory to alkylating agents may respond to VAD-type regimens [5]. Prior attempts to circumvent resistance with cyclosporin resulted in increased toxicity but little or

no additional antimyeloma activity [42]. It has been known for some time that younger patients who fail to respond to VAD as primary therapy prior to planned ASCT, may still respond to ASCT [5]. It is important to also note that following MP treatment, a subgroup of patients who do not reach CR but achieve a non-progressive PR, may enjoy a survival that is equivalent to patients who achieve a stable response [5,23,43].

In younger patients, more intensive combinations, e.g. etoposide, methylprednisolone, cytarabine and cisplatin (ESHAP) or dexamethasone, cyclophosphamide, etoposide, and cisplatin (DCEP) or DTPACE have also been tested may both achieve a response and allow mobilization of stem cells to proceed with ASCT, but are limited by toxicity [5].

Thalidomide alone or in combination with dexamethasone, or with dexamethasone plus cyclophosphamide is active in this setting, and especially in combination. A review on 42 phase II trials of single agent thalidomide in relapsed or refractory disease has been published [44]. In most of these studies, the target dose was 800 mg daily but the median tolerated dose was between 200-400 mg. There was a 29% PR/CR rate in 1629 patients but no clear dose–response relationship. Neuropathy occurred in approximately 30% patients, with VTE risk modest when thalidomide is used alone. As described above, the combination of thalidomide with ASCT and/or cyclophosphamide achieved higher response rates (60%) in relapsed and refractory patients. Most patients who respond to thalidomide-based therapy have a decline in their M-protein after 3-6 weeks, and so to start with thalidomide alone and to add other agents in patients not responding after 3-4 weeks may be a reasonable strategy [5,44].

Immunomodulatory analogs of thalidomide, specifically lenalidomide (Revlimid) and pomalidomide (Actimid, Celgene, USA) appear to have activity similar to that of the parent compound but with markedly greater potency, and combinations of these drugs with steroids chemotherapy are now being evaluated [5]. Significant neuropathy has not been observed with lenalidomide alone, and indeed rates of DVT on monotherapy are low. Dimopoulos and Weber have presented the results of two parallel trials comparing lenalidomide plus high dose dexamethasone vs placebo and high dose dexamethasone in relapsed and refractory myeloma patients. The CR rates were, similar in both studies, (8% vs 1% for the control arm) and the overall response rates were markedly and/or higher among the lenalidomide-treated patients at 53% vs 16% [45]. The platform for these studies was provided by doses and schedules from a large, randomized phase 2 study in which 30 mg once daily eg. 3 weeks with one week off was defined as the optimal dose and schedule. In this study, the addition of dexamethasone was also shown to be beneficial. A prior phase I study had established 25 mg/d as a maximum tolerated dose with promising activity and managable toxicity [46].

Bortezomib is a novel dipeptide boronic acid, which selectively and reversibly inhibits the 26S proteasome and has been approved for relapsed or relapsed, refractory myeloma. It has potent antiproliferative, pro-apoptotic effects (via NF-κB blockade), downregulates the expression of adhesion molecules, inhibits angiogenesis, blocks effectors involved in DNA repair, and disrupts the unfolded protein response, resulting in accumulation of improperly folded proteins and subsequent intense endoplasmic reticular stress with cell death [47].

Two phase 2 studies, SUMMIT and CREST, were designed to evaluate activity in relapsed and relapsed/refractory MM patients. In the SUMMIT trial, patients were treated with bortezomib 1.3 mg/m^2 on days 1, 4, 8 and 11 every 3 weeks, and dexamethasone was added in patients with suboptimal responses to bortezomib alone [22]. The overall response rate was 35%, including 10% CR or near CR, and an OS of 17 months was seen, which was markedly better than expected in such a poor prognostic population [22]. The CREST trial compared two doses of bortezomib (1.3 vs 1.0 mg/m^2) and showed that a reduced dose was able to produce responses in up to one third of the patients with a trend towards a lower toxicity. This study also showed an improvement in response by adding dexamethasone in patients who showed suboptimal response to bortezomib alone with 33% of patients with suboptimal response to monotherapy improving their resonse with the addition of steroid at relatively low dose.

A subsequent randomized phase 3 trial (APEX) included 669 patients with relapsed MM demonstrated that bortezomib is more effective than high-dose dexamethasone demonstrated by a significant improvement in response rate (43% vs 18%), median time to with progression (6.2 vs 3.4 months) and 1-year survival rate (80% vs 67%, respectively) [48]. It is important to note that response with bortezomib is usually rapid (within 1 or 2 cycles), and independent of type and number of previous therapies. Although these results are encouraging, acquired resistance has already been observed, and in vitro synergy of bortezomib with other agents justifies combination therapy. Two pilot studies have shown that bortezomib in combination with melphalan or pegylated liposomal doxorubicin or cyclophosphamide plus dexamethasone produces a response rate of 50% to 76% in refractory MM, including a substantial number of CRs (6 to 30%). Bortezomib has also been combined with thalidomide: Zangari et al have reported in 79 refractory patients (67% prior thalidomide, 95% prior ASCT) the results of this combination [49]. Thalidomide was started at 50 mg/day and increased in a phase-1 fashion up to a maximum dose of 200 mg. Bortezomib was started at 1.0 mg/m^2 and also increased to a maximum of 1.3 mg/m^2. The response rates for patients in the study were 52% (CR + PR), with 17% achieving a VGPR or better. Patients who had not been previously exposed to thalidomide and who received the higher bortezomib dose had superior survival. Toxicity was primarily hematologic, and the incidence of grade 3 or 4 peripheral neuropathy quite low, although the overall incidence of all grades of treatment-emergent neuropathy was approximately 60%, a combination of thalidomide and bortezomib with adriamycin and dexamethasone is also being explored; the CR+PR rate is about 55% and toxicities are manageable. These response rates are clearly superior to those obtained with bortezomib alone [50,51].

The most common side effects of bortezomib, used as monotherapy in refractory patients, include gastrointestinal symptoms, fatigue, and anorexia, although these were mostly grade 1-2. Thrombocytopenia is reversible but can be significant grade 3-4, due to a reversible blockage in platelet release, and is found in 30% of cases, while anemia and neutropenia are un-

common (<10%). The most troublesome side effect is painful/sensory peripheral neuropathy (up to 37%, with 9% grade 3), although this typically resolves or improves in about two-thirds of patients after completion or discontinuation of therapy [18]. Clinicians should be aware that an early reduction of the dose as soon as peripheral neuropathy emerges, according to well-established guidelines, helps to avoid more severe symptoms and the need for interruption of treatment. So far the reported side effects with the combination therapies in newly diagnosed patients are similar to those previously reported in refractory treated patients. Therefore, overall, the toxicity profile of bortezomib is now well defined and most complications are predictable and managable [29]. In addition, there are potential properties of Bortezomib which may be especially important in the treatment of myeloma: activity against extramedullary plasmacytomas, renal failure, and osteoblast inducing activity, making thisagent a very attractive component of most combinations in relapsed, refractory myeloma. [52-54]. The efficacy of novel agents in this setting have been summarized in Table 3.

In terms of the strategies in relapsed disease, ASCT may be considered in patients who have not had a prior stem cell transplant. A second ASCT can also be an effective strategy in selected patients who relapse after an initial autograft, in particular those with a low, 2-microglobulin at salvage, one prior transplant, and late relapse (>12 months). Patients with at least one favourable variable have a projected survival at 18 months of 79%, compared with 38% for patients with unavourable features [5,43,55]. There have as yet been no reported studies comparing a second autograft with other relapse strategies and there is insufficient evidence to routinely recommend allografting as a salvage procedure other than as part of a clinical trial [5,43].

Arsenic trioxide has been used in myeloma but with limited success [56]. Steroids alone may be useful in patients at second or later relapse or in patients at second or later relapse in for whom chemotherapy is otherwise contraindicated, (e.g. due to pancytopenia). Weekly oral or i.v. cyclophosphamide remains a useful regimen for patients [5]. Double hemi-body irradiation is a palliative therapy in patients with widespread bone pain and in those refractory to chemotherapy and steroids, but caution is required as it can cause significant myelosuppression [5].

VI. Role of maintenance therapy

The role of maintenance therapy following the achievement of plateau phase is an area of active investigation both after chemotherapy alone or after stem cell transplantation. A number of studies have examined the therapeutic role of IFN maintenance therapy following induction chemotherapy. A meta-analysis has evaluated individual patient data on 1543 patients in 12 trials where patients were randomised to receive IFN after induction therapy and in a further 2469 patients in 12 trials where patients were randomised to receive IFN in the induction phase (Myeloma Trialists' Collaborative Group, 2001) [5]. Many of those given IFN in induction continued with IFN as maintenance. In patients who received IFN only as maintenance, PFS was significantly improved with a median prolongation of about 6 months, and an increase in 7 months in median OS

Table 3. Efficacy of single agents in relapsed/refractory MM

protocol	phase	number	CR+PR%	CR+nCR%	authors
Bortezomib single (APEX)	3	331	43	16	Richardson[46]
Thalidomide	2	169	30	14	Barlogie[11,37]
Thalidomide	2	42	43	-	Ciberia*
Lenalidomide	2	222	27	-	Richardson[46]
Lenalidomide	2	101	24	6	Richardson[46]
Bortezomib+/-Dexamethasone	1/2	32	67	29(CR)	Solano*
Bortezomib+Dexamethasone	3b	624	54	35	Mikhael*
Thalidomide+Dexamethasone	2	77	41	18	Palumbo[41]
Lenalidomide+Dexamethasone	3	176	59	15	Dimopoulos[45]
Lenalidomide+Dexamethasone	3	170	59	13	Weber *
Bortezomib+Dexamethasone	3b	624	54	35	Mikhael*
Bortezomib+Dexamethasone	1/2	32			Solano*
Bortezomib+ Doxil	3	646	48	14	Orlowski*
Bortezomib+Lenalidomide	1	38	39	6	Richardson*
Bortezomib+Thalidomide+Doxil	2	23	65	23	Chanan-Khan*
Bortezomib+Cyclophosphamide+Prednisone	1/2	27	84	38	Reece*
Bortezomib+Melphalan+Dexamethasone	1/2	53	60	12	Papat*
Bortezomib+Dexamethasone+Cyclophosphamide	1/2	42	64	27(CR)	Davies*
Bortezomib+Melphalan+Prednisone+Thalidomide	1/2	30	81	36	Palumbo*
Bortezomib+Melphalan+Dexa+Thalidomide	2	60	60	11(CR)	Terpos*

* : abstracts from ASH 2005 or 2006

(P = 0.001). However, if all 4066 patents from all 24 trials were analysed together, the gain in median OS for IFN-treated patients was only 4 months. Similar results were obtained in the meta-analysis of published data on IFN trials [55]. Median PFS and OS were prolonged by 4 and 7 months, respectively. If studies where IFN was given as induction were included, the gain in OS was only 3.1 months. A preliminary report on a US Intergroup study showed a lack of benefit for IFN maintenance after both conventional and HDT [23]. Overall, therefore the data do not show significantly better response or survival in any particular patient group and dosages of IFN have varied, but any benefit for doses >3 MU/m^2 s.c. three times per week has not been shown. And data on duration of therapy are limited. Moreover, side effects are challenging [5].

Several newer agents are now being studied as maintenance therapies in plateau phase following initial chemotherapy or ASCT, including thalidomide, lenalidomide and bortezomib.

There are two recently published reports that have used thalidomide in the post ASCT setting: Brinker et al reported improved median survival (65.5 months) in those who received thalidomide compared with those who did not receive thalidomide (44.5 months; p=.09) following ASCT. When they were separated according to reasons for thalidomide use, patients who received thalidomide as maintenance had improved OS compared with patients who received thalidomide as salvage (65 months vs. 54 months; P=.05) [53]. A key second study is an IFM trial led by Michel Attal and colleagues who enrolled 597 patients younger than age 65 years [58]. Patients were randomly assigned to receive no maintenance (arm A), pamidronate (arm B), or pamidronate plus thalidomide (arm C). A complete or very good partial response was achieved by 55% of patients in arm A, 57% in arm B, and 67% in arm C (p = .03). The 3-year postrandomization probability of EFS was 36% in arm A, 37% in arm B, and 52% in arm C (p < .009). The 4-year postdiagnosis probability of survival was 77% in arm A, 74% in arm B, and 87% in arm C (p < 0.04). The proportion of patients who had skeletal events was 24% in arm A, 21% in arm B, and 18% in arm C (p:NS). Thalidomide thus appears to be an effective maintenance therapy in patients with multiple myeloma, but administered the concomitant pamidronate did not decrease the incidence of bone events. Moreover, when patients were analyzed separately according to reasons for thalidomide use, patients who received thalidomide as maintenance had improved OS compared with patients who received thalidomide as salvage (65 months vs. 54 months; P=.05) [58]. Indeed, the patients who had actually gained an advantage from Thalidomide in this trial were those who had not achieved CR with HDT. Thus the use of Thalidomide was more like a consolidation strategy, rather than true maintenance. We would therefore suggest thalidimide for those patients who have achieved less than CR and otherwise should consider delaying its use until progression in those who have attained CR following ASCT. [59]

In the Arkansas total therapy 2 study, relapses in the thalidomide group appeared to be more drug-resistant than relapses in the control group [19]. Superior response rates have been reported for TD as compared with ASCT alone for induction therapy in patients with multiple myeloma. Since many patients in these trials received ASCT after induction therapy with TD, the long-term benefit of this combination cannot be ascertained. Reserving thalidomide for maintenance therapy after transplantation, as was done in the larger trials conducted by the IFM, has several possible advantages: resistance may be avoided; the risk of DVT can be reduced, since this risk is highest during induction therapy, when the burden of tumor is high; the incidence of neurotoxic effects is expected to be reduced with a later introduction of thalidomide at lower doses (50 to 100 mg) during maintenance therapy. Conversely, high rates of CR, approaching the rates observed with ASCT, have recently been achieved in those trials when thalidomide was combined with standard treatment such as MP. Similarly, combinations of bortezomib, dexamethasone and pegylated doxorubicin or thalidomide have shown promise. Although ASCT has considerable transplant related complications, the low mortality and infrequent chronic adverse effects have to be balanced against the potential for chronic adverse effects of the some of newer agents and hopefully ongoing trials will prove informative in this regard.

As almost all patients with myeloma will relapse, the overall management strategy should include plans when and how to treat multiple relapses. Generally, the criteria to initiate treatment during relapse are the same as the initial treatment and it is not recommended to start treatment when patients are in a non-progressive plateau that may last for some time. When signs of symptomatic disease and end organ injury become evident, therapeutic objectives are to achieve rapid disease control, ameliorate symptoms, improve quality of life and prolong survival. While early relapse carries a risk of worse outcome, patients whose disease relapses or progresses after a long plateau phase are likely to respond well to further treatment; survival from relapse/progression may be even longer than the duration of initial remission, but this is of course rare.

Specific aspects of treatment such as approach to bone disease, anemia, neurological problems, renal failure, infections, plasmacytomas and plasma cell leukemia are reviewed separately and readers may refer to recent guidelines prepared in 2005, and published in 2006 [5].

The Future

Novel biologically-based treatment strategies targeting the MM tumor cell and its microenvironment can overcome resistance to current therapies and are now established as an effective group of treatment paradigms which improve patient survival in MM. Many of these agents have multiple biologic activities, which may be advantageous because ubiquitously shared fundamental molecular targets, as have been therapeautically exploited in chronic myelocytic leukemia or acute promyelocytic leukemia, are lacking in MM, with numerous signaling pathways being a hall mark of MM pathobiology. Combinations with conventional and novel agents are showing great promise. Ongoing gene microarray and proteomic studies of these novel agents and their effects in MM are delineating molecular mechanisms of drug sensitivitiy versus drug resistance. These studies will hopefully generate more selective therapies which inturn can be validated preclinically and translated to the bedside in derived clinical trials. Conversely, gene microarray and proteomic studies of tumor, blood, and BM samples from patients

treated in clinical trials involving novel agents will potentially define in-vivo targets conferring drug sensitivity and resistance and provide the framework for the development of more selevctive, potent, and less toxic next-generation targeted therapies. These studies will also establish the pre-clinical rationale for combining novel and conventional therapies and allow for selection of patients more likely to respond, with the overall goal of continued improvement in outcome.

References

1. Kyle R A, Five decades of therapy for multiple myeloma: a paradigm for therapeutic models.Leukemia. 2005;19:910-2.
2. Ösby E, Beksac M, Reizenstein P.Alternating combination chemotherapy does not delay development of refractoriness in myeloma. Anticancer Res. 1986;6:1145-7.
3. Kyle, R.A, Rajkumar S V (2004). Multiple Myeloma. NEJM 351: 1860 -73.
4. Kumar A.,Loughran T.,Alsina M. Durie B. Management of multiple myeloma: a systematic review and critical appraisal of published studies. Lancet Oncol. 2003;4:293-304.
5. Smith A., Wisloff F., Samson D.,on behalf of the UK Myeloma Forum, Nordic Myeloma Study Group and British Committee for Standards in haematology Guidelines on the diagnosis and management of multiple myeloma 2005.Br J Haematol 2006;132:410-51.
6. Durie BG, Harousseau JL, Miguel JS, Blade J, Barlogie B, Anderson K, Gertz M, Dimopoulos M, Westin J, Sonneveld P, Ludwig H, Gahrton G, Beksac M, Crowley J, Belch A, Boccadaro M, Cavo M, Turesson I, Joshua D, Vesole D, Kyle R, Alexanian R, Tricot G, Attal M, Merlini G, Powles R, Richardson P, Shimizu K, Tosi P, Morgan G, Rajkumar SV; International Myeloma Working Group . International uniform response criteria for multiple myeloma. Leukemia. 2006;20:1467-73.
7. Blade J, Samson D, Reece D, Apperley J, Björkstrand B, Gahrton G, Gertz M, Giralt S, Jagannath S, Vesole D. Criteria for evaluating disease response and progression in patients with multiple myeloma treated by high-dose therapy and haemopoietic stem cell transplantation. Br J Haematol 1998;102:1115-23.
8. Attal M, Harousseau JL, Stoppa AM, Sotto JJ, Fuzibet JG, Rossi JF, Casassus P, Maisonneuve H, Facon T, Ifrah N, Payen C, Bataille R. A prospective, randomized trial of autologous bone marrow transplantation and chemotherapy in multiple myeloma. N Engl J Med 1996;335:91-7.
9. Child JA, Morgan GJ, Davies FE, Owen RG, Bell SE, Hawkins K, Brown J, Drayson MT, Selby PJ; Medical Research Council Adult Leukaemia Working Party. High-Dose Chemotherapy with Hematopoietic Stem-Cell Rescue for Multiple Myeloma. N Engl J Med 2003;348:1875-83.
10. Palumbo A, Bringhen S, Petrucci MT, Musto P, Rossini F, Nunzi M, Lauta VM, Bergonzi C, Barbui A, Caravita T, Capaldi A, Pregno P, Guglielmelli T, Grasso M, Callea V, Bertola A, Cavallo F, Falco P, Rus C, Massaia M, Mandelli F, Carella AM, Pogliani E, Liberati AM, Dammacco F, Ciccone G, Boccadoro M. Intermediate-dose melphalan improves survival of myeloma patients aged 50 to 70: results of a randomized controlled trial. Blood 2004;104:3052-7.
11. Barlogie B, Kyle RA, Anderson KC, Greipp PR, Lazarus HM, Hurd DD, McCoy J, Moore DF Jr, Dakhil SR, Lanier KS, Chapman RA, Cromer JN, Salmon SE, Durie B, Crowley JC. Standard Chemotherapy Compared With High-Dose Chemoradiotherapy for Multiple Myeloma: Final Results of Phase III US Intergroup Trial S9321. J Clin Oncol 2006;24: 929-36.
12. Blade, J., Rosinol, L., Sureda A., et al. High-dose therapy intensification compared with continued standard chemotherapy in multiple myeloma patients responding to the initial chemotherapy: long-term results from a prospective randomized trial from the Spanish cooperative group PETHEMA. Blood 2005;106: 3755-9.
13. Rajkumar SV, Blood E, Vesole D, Fonseca R, Greipp PR; Eastern Cooperative Oncology Group. Phase III clinical trial of thalidomide plus dexamethasone compared with dexamethasone alone in newly diagnosed multiple myeloma: a clinical trial coordinated by the Eastern Cooperative Oncology Group.J Clin Oncol. 2006;24:431-6.
14. Cavo M, Zamagni E, Tosi P, Tacchetti P, Cellini C, Cangini D, de Vivo A, Testoni N, Nicci C, Terragna C, Grafone T, Perrone G, Ceccolini M, Tura S, Baccarani M; Bologna 2002 study. Superiority of thalidomide and dexamethasone over vincristine-doxorubicindexamethasone (VAD) as primary therapy in preparation for autologous transplantation for multiple myeloma. Blood. 2005;106:35-9.
15. Macro M, Divine M, Uzunhan Y, Jaccard A, Bouscary D, Leblond V, Janvier M, Genet P, Castaigne S, Royer B, Allard C, Chevret S, Fermand JP. Dexamethasone+Thalidomide (Dex/Thal) Compared to VAD as a Pre-Transplant Treatment in Newly Diagnosed Multiple Myeloma (MM): A Randomized Trial. Blood 2006;108:57a.
16. Cavo M, Testoni N, Terragna C, Zamagni E, Tacchetti P, Nicci C, Renzulli M, Montanari E, Perrone G, Cangini D, Grafone T, Ceccolini M, Brioli A M, Martinelli G, Tosi P, Baccarani M. Up-Front Thalidomide-Dexamethasone (THAL) and Double Autologous Transplantation (Double TX) for Multiple Myeloma: Comparison with Double TX without Added Thalidomide and Prognostic Implications of Chromosome 13 Deletion and Translocation t(4;14). Blood 2006;108:3081a.
17. Goldschmidt H, Sonneveld P, Breitkreuz I, van der Holt B, Benner A,. Barge R M.Y, Salwender H, Bos G M.J., Glasmacher A, Raymakers R, Scheid C, Huijgens PC., Naumann R, van Oers M H.J., Hänel A, Vellenga E, Martin H, Wijermans P W., Ho A D., Westveer P H.M., Verhoef, G E.G. Mazitschek U, Lokhorst H M. .HOVON 50/GMMG-HD3-Trial: Phase III Study on the Effect of Thalidomide Combined with High Dose Melphalan in Myeloma Patients up to 65 Years. Blood 2005:106:424a.
18. Richardson P, Anderson K.Thalidomide and dexamethasone: a new standard of care for initial therapy in multiple myeloma. J Clin Oncol. 2006;24:334-6.
19. Barlogie B, Tricot G, Anaissie E, Shaughnessy J, Rasmussen E, van Rhee F, Fassas A, Zangari M, Hollmig K, Pineda-Roman M, Lee C, Talamo G, Thertulien R, Kiwan E, Krishna S, Fox M, Crowley J. Thalidomide and Hematopoietic-Cell Transplantation for Multiple Myeloma. New Engl J Med 2006;354:1021-30.
20. Lokhorst HM, Schmidt-Wolf I, Sonneveld P, van der Holt B, Martin H, Barge R, Bertsch U, Schlenzka J, Bos GM, Croockewit S, Zweegman S, Breitkreuz I, Joosten P, Scheid C, van Marwijk-Kooy M, Salwender HJ, van Oers MH, Schaafsma R, Naumann R, Sinnige H, Blau I, Verhoef G, de Weerdt O, Wijermans P, Wittebol S, Duersen U,Vellenga E, Goldschmidt H; Dutch-Belgian HOVON; German GMMG. Thalidomide in induction treatment increases the very good partial response rate before and after high-dose therapy in previously untreated multiple myeloma. Haematologica. 2008;93:124-7.
21. Harousseau J L, Marit G,Caillot D, Casassus P, Facon T, Mohty M, Maloisel F, Maisonneuve H, Chaleteix C, Benboubker L, Esseltine D L, Attal M. VELCADE/Dexamethasone (Vel/Dex) Versus VAD as Induction Treatment Prior to Autologous Stem Cell Transplantation (ASCT) in Newly Diagnosed Multiple Myeloma (MM): An Interim Analysis of the IFM 2005-01 Randomized Multicenter Phase III Trial. Blood 2006,108:56a.
22. Richardson P. G., Barlogie B., Berenson J., Singhal S., Jagannath S., Irwin D., Rajkumar S. V., Srkalovic G., Alsina M., Alexanian R., Siegel D., Orlowski R. Z., Kuter D., Limentani S. A., Lee S., Hideshima T., Esseltine D.L., Kauffman M., Adams J., Schenkein D. P., Anderson K. C. A Phase 2 Study of Bortezomib in Relapsed, Refractory Myeloma. N Engl J Med 2003;348:2609-17.
23. Durie BG, Jacobson J, Barlogie B, Crowley J. Magnitude of response with myeloma frontline therapy does not predict outcome: importance of time to progression in southwest oncology group chemotherapy trials. J Clin Oncol. 2004;22:1857-63.
24. Kyle R., Leong T., Li S., et al. Complete response in multiple myeloma clinical trial E9486, an Eastern Cooperative Oncology Group study not involving stem cell transplantation. Cancer 2006;106:1958-66.
25. Dispenzieri A.,Blood E.,Vesole D. Etal. A phase II study of PS-341 for patients with high risk newly diagnosed multiple myeloma: a trial of the Eastern Coopertaive Group (E2A02). Blood 2005;106:2546a Barlogie B, Tricot G. Complete response in myeloma: a Trojan horse? Blood 2006:108: 2134.
26. Jagannath S, Durie BG, Wolf J, Camacho E, Irwin D, Lutzky J, McKinley M, Gabayan E, Mazumder A, Schenkein D, Crowley J. Bortezomib therapy alone and in combination with dexamethasone for previously untreated symptomatic multiple myeloma. Br J Haematol. 2005;129:776-83.
27. Harousseau JL, Attal M, Leleu X, Troncy J, Pegourie B, Stoppa AM, Hulin C, Benboubker L, Fuzibet JG, Renaud M, Moreau P, Avet-Loiseau H. Bortezomib plus dexamethasone as induction treatment prior to autologous stem cell transplantation in patients with newly diagnosed multiple myeloma: results of an IFM phase II study. Haematologica 2006;91:1498-505.
28. Oakervee HE, Popat R, Curry N, Smith P, Morris C, Drake M, Agrawal S, Stec J, Schenkein D, Esseltine DL, Cavenagh JD. PAD combination therapy (PS-341/bortezomib, doxorubicin and dexamethasone) for previously untreated patients with multiple myeloma. Br J Haematol. 2005;129:755-62.

29. San-Miguel J, Bladé J. Perspective on the current use of bortezomib in multiple myeloma.Haematologica 2006;91:871.
30. Rajkumar SV, Hayman SR, Lacy MQ, Dispenzieri A, Geyer SM, Kabat B, Zeldenrust SR, Kumar S, Greipp PR, Fonseca R, Lust JA, Russell SJ, Kyle RA, Witzig TE,Gertz MA.Combination therapy with lenalidomide plus dexamethasone (Rev/Dex) for newly diagnosed myeloma.Blood. 2005;106:4050-3.
31. Cavo M, Baccarani M, The Changing Landscape of Myeloma Therapy. New Engl J Med 2006:354(10): 1076-1078.
32. Facon T, Mary JV., Pégourie B. et al. Dexamethasone-based regimens versus melphalan-prednisone for elderly multiple myeloma patients ineligible for high-dose therapy .Blood, 2006;107:1292-8.
33. Palumbo A, Bringhen S, Caravita T, Merla E, Capparella V, Callea V, Cangialosi C, Grasso M, Rossini F, Galli M, Catalano L, Zamagni E, Petrucci MT, De Stefano V, Ceccarelli M, Ambrosini MT, Avonto I, Falco P, Ciccone G, Liberati AM, Musto P, Boccadoro M; Italian Multiple Myeloma Network, GIMEMA. Oral melphalan and prednisone chemotherapy plus thalidomide compared with melphalan and prednisone alone in elderly patients with multiple myeloma: randomised controlled trial.Lancet 2006;367:825-31.
34. Facon T, Mary J.Y., Hulin C., Benboubker L., Attal M., Renaud M., Harousseau J.L., Pegourie B., Guillerm G., Chaleteix C., Dib M., Voillat L., Maisonneuve H., Troncy J., Dorvaux V., Monconduit M., Martin C., Casassus P., Jaubert J., Jardel H., Kolb B Bauters F., Melphalan and prednisone plas thalidomide versus melphalan and prednisone alone or reduced-intensity autologous stan cell transplantation in elderly patients with Multiple Myeloma (IFM 99-06): a randomised trial. Lancet 2007;370: 1209-18.
35. Mateos MV, Hernández JM, Hernández MT, Gutiérrez NC, Palomera L, Fuertes M, Díaz-Mediavilla J, Lahuerta JJ, de la Rubia J, Terol MJ, Sureda A, Bargay J, Ribas P, de Arriba F, Alegre A, Oriol A, Carrera D, García-Laraña J, García-Sanz R, Bladé J, Prósper F, Mateo G, Esseltine DL, van de Velde H, San Miguel JF. Bortezomib plus melphalan and prednisone in elderly untreated patients with multiple myeloma: results of a multicenter phase 1/2 study Blood, 2006;108:2165-72.
36. Offidani M, Corvatta L, Piersantelli MN, Visani G, Alesiani F, Brunori M, Galieni P, Catarini M, Burattini M, Centurioni R, Ferranti M, Rupoli S, Scortechini AR, Giuliodori L, Candela M, Capelli D, Montanari M, Olivieri A, Poloni A, Polloni C, Marconi M, Leoni P.Thalidomide, dexamethasone, and pegylated liposomal doxorubicin (ThaDD) for patients older than 65 years with newly diagnosed multiple myeloma. Blood, 2006;108: 2159-64 .
37. Barlogie B, Desikan R, Eddlemon P, Spencer T, Zeldis J, Munshi N, Badros A, Zangari M, Anaissie E, Epstein J, Shaughnessy J, Ayers D, Spoon D, Tricot G. Extended survival in advanced and refractory multiple myeloma after single-agent thalidomide: identification of prognostic factors in a phase 2 study of 169 patients Blood. 2001;98:492-4
38. Singhal S, Mehta J, Desikan R, Ayers D, Roberson P, Eddlemon P, Munshi N, Anaissie E, Wilson C, Dhodapkar M, Zeddis J, Barlogie B. Antitumor activity of thalidomide in refractory multiple myeloma. N. Engl. J. Med. 1999 18;341:1565-71.
39 Jagannath S, Richardson PG, Sonneveld P, Schuster MW, Irwin D, Stadtmauer EA, Facon T, Harousseau JL, Cowan JM, Anderson KC. Bortezomib appears to overcome the poor prognosis conferred by chromosome 13 deletion in phase 2 and 3 trials. Leukemia 2007;21:151-7.
40. Chang H, Trieu Y, Qi X, Xu W, Stewart KA, Reece D.Bortezomib therapy response is independent of cytogenetic abnormalities in relapsed/refractory multiple myeloma.Leuk Res. 2007;31:779-82.
41. Palumbo A, Falco P, Falcone A, Corradini P, Di Raimondo F, Giuliani N, Rossi G, Morabito F, Canepa L, Gozzetti A, Ambrosini M T, Zeldis J, Knight R, Foà R, Boccadoro M, Petrucci M T. Oral Revlimid® Plus Melphalan and Prednisone (R-MP) for Newly Diagnosed Multiple Myeloma: Results of a Multicenter Phase I/II Study. Blood 2006,108:800a.
42. Sonneveld P, Suciu S, Weijermans P, Beksac M, Neuwirtova R, Solbu G, Lokhorst H, van der Lelie J, Dohner H, Gerhartz H, Segeren CM, Willemze R, Lowenberg B; European Organization for Research and Treatment of Cancer (EORTC); Leukaemia Cooperative Group (LCG); Dutch Haemato-Oncology Cooperative Study Group (HOVON). Cyclosporin A combined with vincristine, doxorubicin and dexamethasone (VAD) compared with VAD alone in patients with advanced refractory multiple myeloma: an EORTC-HOVON randomized phase III study (06914).Br J Haematol. 2001;115:895-902.
43. Hari P, Pasquini MC, Vesole DH. Cure of multiple myeloma -- more hype, less reality.Bone Marrow Transplant. 2006;37:1-18.
44. Glasmacher A, Hahn C, Hoffmann F, Naumann R, Goldschmidt H, von Lilienfeld-Toal M, Orlopp K, Schmidt-Wolf I, Gorschluter M. A systematic review of phase-II trials of thalidomide monotherapy in patients with relapsed or refractory multiple myeloma. Br J Haematol. 2006;132:584-93.
45. Dimopoulos, M A, Spencer A, Attal M, , Prince M, Harousseau JL,, Dmoszynska A, Yu Z, Olesnyckyj M, Zeldis J, Knight R, .Study of Lenalidomide Plus Dexamethasone Versus Dexamethasone Alone in Relapsed or Refractory Multiple Myeloma (MM): Results of a Phase 3 Study (MM-010). 2005 106(11): Abstract 6a.
46. Richardson PG, Blood E, Mitsiades CS, Jagannath S, Zeldenrust SR, Alsina M, Schlossman RL, Rajkumar SV, Desikan KR, Hideshima T, Munshi NC, Kelly-Colson K, Doss D, McKenney ML, Gorelik S, Warren D, Freeman A, Rich R, Wu A, Olesnyckyj M, Wride K, Dalton WS, Zeldis J, Knight R, Weller E, Anderson KC. A randomized phase 2 study of lenalidomide therapy for patients with relapsed or relapsed and refractory multiple myeloma.Blood. 2006;108:3458-64.
47. Hideshima T, Richardson P, Chauhan D, Palombella VJ, Elliott PJ, Adams J,Anderson KC. The proteasome inhibitor PS-341 inhibits growth, induces apoptosis, and overcomes drug resistance in human multiple myeloma cells. Cancer Res. 2001;1; 61:3071-6.
48. Richardson P. G., Sonneveld P., Schuster M. W., Irwin D., Stadtmauer E. A., Facon T., Harousseau J.-L., Ben-Yehuda D., Lonial S., Goldschmidt H., Reece D., San-Miguel J. F., Bladé J., Boccadoro M., Cavenagh J., Dalton W. S., Boral A. L., Esseltine D. L., Porter J. B., Schenkein D., Anderson K. C., the Assessment of Proteasome Inhibition for Extending Remissions (APEX) Investigators. Bortezomib or high dose dexamethasone for relapsed myeloma. N Engl J Med 2005;352:2487-98.
49. Wang M, Delasalle K , Giralt S, Alexanian R, Rapid Control of Previously Untreated Multiple Myeloma with Bortezomib-Thalidomide-Dexamethasone Followed by Early Intensive Therapy. Blood 2005;106:784a.
50. Chanan-khan A A, Padmanabhan S, Miller K C, Musiel L,Yu J, Bernstein Z P, Manochakian R, Czuczman M S, .Final Results of a Phase II Study of Bortezomib (Velcade) in Combination with Liposomal Doxorubicin (Doxil) and Thalidomide (VDT) Demonstrate a Sustained High Response Rates in Patients (pts) with Relapsed (rel) or Refactory (ref) Multiple Myeloma. Blood 2006,108:3539a.
51. Harousseau J L, Nagler A, Sonneveld P, Bladé J, Hajek R, Spencer A, Robak T, Xiu L, Zhuang S H, Orlowski R Z. Effect of the combination of pegylated liposomal doxorubicin and bortezomib on time to progression (TTP) and overall survival of patients with relapsed/refractory multiple myeloma compared with bortezomib alone.J Clin Oncol 2007,25: 8002.
52. Heider U, Kaiser M, Müller C, Jakob C, Zavrski I, Schulz CO, Fleissner C, Hecht M, Sezer O. Bortezomib increases osteoblast activity in myeloma patients irrespective of response to treatment. Eur J Haematol. 2006;77:233-8.
53. Zangari M, Esseltine D, Lee CK, Barlogie B, Elice F, Burns MJ, Kang SH, Yaccoby S, Najarian K, Richardson P, Sonneveld P, Tricot G. Response to bortezomib is associated to osteoblastic activation in patients with multiple myeloma. Br J Haematol. 2005;131:71-3.
54. Laura R, Cibeira MT, Uriburu C, Yantorno S, Salamero O, Bladé J, Montserrat E. Bortezomib: an effective agent in extramedullary disease in multiple myeloma. Eur J Haematol. 2006;76:405-8.
55. Fritz E, Ludwig H. Interferon-alpha treatment in multiple myeloma: meta-analysis of 30 randomised trials among 3948 patients. Ann Oncol. 2000;11:1427-36.
56. Wu KL, Beksac M, van Droogenbroeck J, Amadori S, Zweegman S, Sonneveld P, Phase II multicenter study of arsenic trioxide, ascorbic acid and dexamethasone in patients with relapsed or refractory multiple myeloma.. Haematologica. 2006;91:1722-3.
57. Brinker BT, Waller EK, Leong T et al. Maintenance therapy with thalidomide improves overall survival after autologous hematopoietic progenitor cell transplantation for multiple myeloma. Cancer 2006;106:2171-80.
58. Attal M, Harousseau JL, Leyvraz S, Doyen C, et al. Maintenance therapy with thalidomide improves survival in multiple myeloma patients. Blood 2006;108:3289-94
59. Alvares CL, Davies FE, Horton C, Patel G, Powles R, Morgan GJ. The role of second autografts in the management of myeloma at first relapse.Haematologica. 2006;91:141-2.
60. Barlogie B., Anaissie E., Haessler J., van Rhee F., Pineda-Roman M., Hollmig K., Alsayed Y., Epstein J., Shaughnessy J. D., Cowleg J. Complete remission sustained 3 years from treatment initiation is a powerful surrogate for extended survival in Multiple Myeloma. Cancer. 2008: a head of publication.