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ПРЕГЛЕД ЛИТЕРАТУРЕ / REVIEW ARTICLE

Timing of the High-Dose Therapy in the Area of New Drugs

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SUMMARY
The treatment approach in patients with multiple myeloma (MM) has been essentially changed with introduction of novel agents such as thalidomide, bortezomib and lenalidomide. In patients eligible for autologous stem cell transplant, combinations of novel agents with chemotherapy have been recognized as induction regimens. New induction regimens have significantly increased the rate of complete remission before and after autologous stem cell transplant with positive impact on the length of progression-free survival followed by the possibility for further improvement with the application of consolidation or use of thalidomide and lenalidomide as maintenance therapy. These results offer new perspectives in the treatment of MM with a reasonable hope of cure.
Keywords: multiple myeloma; autologous haematopoietic stem cell transplantation; new drugs

INTRODUCTION

Multiple myeloma (MM) is a malignancy of plasma cells and is the second most common haematological neoplasia. The incidence rate in Northern Europe is 4-5/100,000 per year. Approximately 3,500 cases are diagnosed in Germany each year. Myeloma remains almost uniformly fatal. As the disease tends to progression, morbidity and eventual mortality are caused by impaired immunodeficiency, skeletal destruction, anaemia and renal failure. The use of high-dose chemotherapy (HDT) and autologous stem cell transplantation (ASCT) has improved the remissions rates in the 90s (Table 1). The 5-year survival rate for patients with myeloma treated with conventional chemotherapy was 25%, whereas intensified therapy increases this rate up to 50% [1]. During the last decade, HDT supported by ASCT has been considered the standard of care for frontline therapy of patients up to the age of 70 years. However, ASCT is not curative and most patients relapse. Thus, the introduction of the novel agents Thalidomide, Bortezomib, and Lenalidomide was a logical step to improve HDT results, and an increase of response and survival has been reported. On the other hand, the use of novel agents as frontline therapy in combination with either Dexamethasone or alkylating agents yields complete remission (CR) and progression-free survival (PFS) rates that are comparable to those achieved with historical ASCT [2]. Therefore, the role of ASCT is again a matter of debate: should it be used as frontline therapy or only as salvage treatment in patients initially treated with novel agents?

HISTORICAL RESULTS AND STANDARD OF CARE IN MULTIPLE MYELOMA IN GERMANY

Conventional therapy

From 1962 until 2004/5 intermittent dosing of the combination Melphalan plus Prednisone (MP) was the treatment of choice. Despite many trials investigating different combinations of conventional chemotherapeutic agents during this time, none were shown to be associated with a significant improvement in overall sur-

Table 1. Association between maximal response and overall survival in patients with newly diagnosed MM treated with ASCT

Prospective study	Maximal response	
	Comparison	P
IFM90	CR/VGPR vs. PR vs. Other	<0.00001
MRC VII	CR vs. PR vs. MR	0.00002
TT1	CR vs. PR	0.2496
TT2	CR vs. PR/NR	<0.05
IFM94-02	Maximal response	<0.001
IFM99C	CR/VGPR vs. PR	<0.0000
NMSG 5/94	CR vs. PR/NR	0.38
Bologna	≥ VGPR vs. Other	0.002
GMA	CR/MRD vs. Other	0.22
Meta-analysis	CR/VGPR vs. PR vs. Other	<0.00001

IFM – Intergroup Francophone du Myelome, France; MRC – Medical Research Council, United Kingdom; TT1/TT2 – total therapy 1/2; NMSG – Nordic Myeloma Study Group; GMA – Group Myelome-Autogreffe, France

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vival (OS) compared to the original MP regimen. Between 50% and 60% of patients respond to conventional chemotherapy while only a minority (<5%) of patients achieves a complete remission. The median overall survival in these studies was less than 3 years. Superior efficacy with regard to both progression-free survival and overall survival has however been demonstrated by the addition of either Bortezomib or Thalidomide to the original MP regimen. Therefore, MP alone is no longer the standard of care in patients aged 65 years or older or for younger patients not being eligible for HDT followed by ASCT [3]. Phase I/II trial data suggest that adding Lenalidomide to MP is also an effective treatment option. At the ASH meeting 2009 first results of a large phase III trial showed a benefit in terms of PFS for MP-Lenalidomide when comparing MP versus MP-Lenalidomide followed by Lenalidomide maintenance treatment. Therapies based on the combination of Dexamethasone and novel agents have also been shown to prolong event-free survival (EFS) and OS in MM patients.

Autologous transplantation

High-dose chemotherapy for MM was introduced in 1983 and showed for the first time that complete remissions could be induced in a substantial percentage of patients. Morbidity and mortality, however, remained high until the implementation of autologous stem cell rescue. Since it was demonstrated that cytokines could be used to mobilize stem cells into the peripheral blood, there has been a huge rise in the use of this treatment modality. Initial evidence of benefit in a single centre non-randomized series [4] was later followed by confirmation in multi-centre prospective randomized clinical trials.

The French and Italian cooperative consortia performed 2 phase III studies comparing single versus double autologous transplantation and found that a second ASCT only appeared to be beneficial in patients who did not achieve CR or VGPR after the first transplant. It should however be emphasized that both studies were not specifically designed to address the impact of remission-status after HDT. The impact of CR after HDT followed by ABSCT was pointed out in the review by Harousseau [5].

Autologous transplantation and new drugs

Induction therapy

For many years, VAD-like regimens (Vincristine, Adriamycin, and Dexamethasone) were the standard induction chemotherapy for MM patients undergoing stem cell transplantation [6]. Although phase II studies showed overall response rates (ORRs) ranging from 55-60%, few patients achieved complete responses (CR) which was presented by Goldschmidt and Sonneveld on the ASH meeting 2006 and in the year 2008. In general, patients induced with VAD required subsequent ASCT before achieving CR. Recent efforts have focused on improving response rates, and in particular CR rates, by the use of novel agents in the upfront setting. A number of such studies involving Thalidomide, Bortezomib or Lenalidomide are summarized below.

Initial induction studies confirmed the superiority of Thalidomide and Dexamethasone to VAD and Dexamethasone alone in terms of the ORR. However, few patients achieved CR (7–13%) [7].

Thalidomide has been also investigated as a component of three-drug regimens. The HOVON50/GMMG-HD3 study investigated the use of Thalidomide in combination with Doxorubicin (Adriamycin) and Dexamethasone (TAD) in a randomized trial [8]. The TAD regimen resulted in significantly higher response rates compared to VAD: CR+VGPR 33% vs. 15% (P<0.001), ≥PR 72% vs. 54% (P<0.001) [9]. In the HOVON-data analysis there was a significant improvement in EFS and PFS in the TAD arm: EFS 33 months vs. 22 months (P<0.001) and PFS 33 months vs. 25 months (P<0.001) for TAD vs. VAD, respectively. However, there was no difference in overall survival between the two arms: 59 months for TAD vs. 62 months for VAD (P=0.96) [10]. Similar results were found in the GMMG-HD3-trial (Figure 1).

The combination of Bortezomib and Dexamethasone as induction therapy has been examined by the French Myeloma Study Group (IFM) in 482 patients in a randomized phase III study [11]. In the IFM 2005/01 trial, patients were randomized to receive four cycles of VAD or four cycles of Bortezomib and Dexamethasone followed by Melphalan 200 mg/m^2 and ASCT. The results of this study demonstrated a significant advantage for Bortezomib and Dexamethasone compared to the VAD regimen: the ORR was 82% for Bortezomib and Dexamethasone as opposed to 65% for VAD (P<0.0001), with CR/nCR rates of 15% and 7%, respectively (P=0.0035) and CR + VGPR rates of 39% and 16%, respectively (P<0.0001). There was a significant difference between the two arms in the 2-year PFS (Bortezomib and Dexamethasone 69% vs. VAD 60%, P=0.0115), while 2-year OS was comparable in the two arms (90% vs. 88%, P=0.4689).

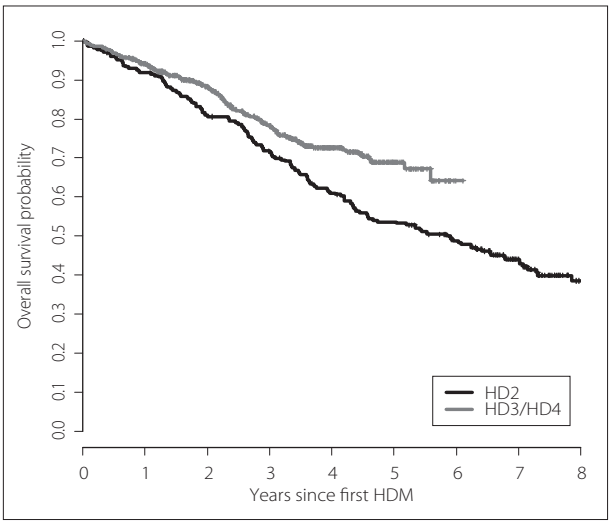

Figure 1. Overall survival in patients from the GMMG-HD2 trial versus patients from the GMMG-HD3/HD4 trial

The ongoing phase III HOVON 65 MM/GMMG-HD4 trial is investigating PAD (Bortezomib, Adriamycin, Dexamethasone) induction therapy in a randomized comparison with VAD followed by either Bortezomib or Thalidomide maintenance treatment post-ASCT. The PAD combination was significantly superior to VAD in terms of VGPR and PR rates. Following the first ASCT, PAD was significantly superior to VAD in terms of CR/nCR, ≥VGPR and PR rates. Although the CR/nCR following PAD induction was unexpectedly low at 7%, it was found to increase during the course of treatment to 26% after the first ASCT and to 43% as best response during Bortezomib maintenance treatment. The combination of PAD was generally well tolerated and more than 80% of patients received the full planned course of PAD. There was no difference in haematological toxicities between VAD and PAD. PAD, however, was associated with a higher incidence of grade 3/4 neuropathy compared to VAD (16% vs. 6%) [12].

The combination of Bortezomib, Cyclophosphamide and Dexamethasone (VCD) has been found to be very active in the relapsed/refractory setting [13] and was also found to result in high response rates in a phase II study investigating this combination as induction therapy [14].

An ongoing phase II/III trial by the German DSMM study group is investigating VCD as induction regimen in 400 patients [15]. The results of an interim analysis involving 200 patients demonstrated an ORR of 84% and a CR rate of 12.5%. Response to treatment was found to be independent of the presence of 'high-risk' cytogenetic abnormalities. The combination was found to be well tolerated with a low overall incidence of neuropathy (12.5%) and a particularly low rate of severe neuropathy (grade 3 0.5%). Furthermore, a low mortality rate (1%) and a low risk of hospitalization due to infection were detected.

A large phase 3 ECOG trial is currently investigating the use of Lenalidomide in combination with two different doses of Dexamethasone in the upfront setting. Patients are randomized to receive Lenalidomide at 25 mg on days 1-21 and high-dose Dexamethasone (40 mg days 1–4, 9–12, and 17–20 every 28 days [RD]) or low-dose Dexamethasone (40 mg days 1, 8, 15, and 22 every 28 days [Rd]) [16, 17]. The primary aim of the study was to compare response of the two regimens after four cycles. The analysis revealed that the RD regimen was associated with a superior ORR and ≥VGPR-rate compared to Rd (ORR 79% vs. 68%, P=0.008; ≥VGPR 42% vs. 24%, P<0.008). Best responses, including ORR (81% vs. 70%; P=0.009) and ≥VGPR (51% vs. 40%; P=0.04), were also significantly higher in the high-dose Dexamethasone arm. Despite this difference in response to treatment, there was no statistical difference in PFS and time to progression (TTP) in the final interpretation. The 3-year OS was 75% in both arms. Among patients who underwent transplantation after four cycles of primary treatment, 3-year OS was 92% compared with <60% in those patients who did not undergo transplantation.

The reduction of the Dexamethasone dose in induction treatment in upcoming trials should be envisioned to decrease toxicity, especially infections, compared to induction regimens with high-dose Dexamethasone. During the induction treatment of the GMMG-HD4 trial (German part of the GMMG-HD4/HOVON65 trial) serious infections (fulfilling the criteria of a serious adverse event) in approx. 20% of patients both in PAD and VAD could be detected. Fatal infections occurred in 3 of 4 deceased patients in PAD and 5 of 7 deceased patients in VAD.

Novel agents in the high dose regimen

In lab studies Bortezomib has shown synergistic effects with alkylating agents. Clinical studies about a combination of high-dose Melphalan plus Bortezomib as preparative regimen prior to ASCT have been performed by Hollmig et al. [18]. This group showed the feasibility of this combination, even if Bortezomib was administered partly after stem cell infusion. A phase II study, conducted by the IFM in 52 patients with de novo myeloma, reported an impressive response rate 3 months after ASCT: 68% VGPRs, including 38% CRs. These results are encouraging and justify further phase III studies [19, 20].

Consolidation and maintenance therapy

There are currently no guidelines concerning post-ASCT therapy [21]. Thalidomide maintenance post-ASCT has been investigated in a number of randomized trials which have led to different results. In two studies, Thalidomide maintenance treatment was associated with a statistically significant improvement in PFS and OS [22, 23]. For example, in the "Spencer-study" comparing Prednisolone and Thalidomide as opposed to Prednisolone alone administered for 12 months following a single ASCT, the Thalidomide-containing maintenance regimen resulted in a significantly superior 3-year PFS (42% vs. 23%, P<0.001) and 3-year OS (86% vs. 75%, P=0.004) compared to Prednisolone. In addition, there was no significant difference in OS 12 months after disease progression (79% vs. 77%; P=0.237), indicating that Thalidomide treatment did not result in a larger proportion of patients with resistant disease.

The addition of Thalidomide in Total Therapy 2, which consisted of double ASCT with Thalidomide given from diagnosis until disease progression, did not prolong OS at a median follow-up of 42 months [24]. Furthermore, in patients who received Thalidomide, survival after relapse was significantly reduced compared to those who had not received Thalidomide. However, with longer follow-up (median 72 months), survival in the Thalidomide arm was found to be superior to that in the control arm. In patients with cytogenetic abnormalities, the difference was statistically significant [25]. A recent analysis of the effect of maintenance therapy in the MRC IX study revealed that Thalidomide treatment was associated with a prolongation of PFS in patients who achieved less than VGPR post-induction indicating a consolidation rather than a maintenance effect. No benefit in OS was observed due to early progress after relapse in those who had received

Thalidomide. It is also notable that Thalidomide maintenance appeared to have a negative impact on survival in patients with del17p in a recent trial.

A trial conducted by Ludwig et al. evaluated Thalidomide and Interferon (Thal-IFN) compared to Interferon (IFN) alone in elderly patients who had previously undergone a first randomization step to either Thal/Dex or MP induction therapy [26]. Of 289 patients who had been through the initial randomization step, 135 achieved at least stable disease and were therefore eligible to undergo subsequent randomization between the two maintenance arms. PFS was significantly longer with Thal-IFN maintenance treatment compared to IFN alone (24 vs. 12.6 months, P<0.024), but OS was similar in the two arms (52.6 vs. 52.2 months, P=0.68). Neurotoxicity, constipation and skin toxicity were significantly more frequent in the Thal-IFN group.

In the HOVON50 and GMMG-HD3 trial Thalidomide 50 mg per day was given as maintenance after HDT followed by ASCT. In both trials PFS was prolonged and OS was not different in the Thalidomide containing induction and maintenance treatment arm.

In the HOVON-analysis [10] prognosis of patients developing relapses in the Thalidomide maintenance arm was inferior to patients treated with IFN. In summary Thalidomide after HDT improves response and PFS. Results in terms of the impact of Thalidomide maintenance on OS are different. The optimal duration and dosage of Thalidomide after HDT is not yet known. Trials comparing Thalidomide as consolidation versus Thalidomide maintenance will be necessary in the future.

The role of Bortezomib in the setting of maintenance and consolidation has been investigated in two small studies [27, 28]. According to a report of Ladetto et al. presented on the ASH meeting 2009 preliminary data suggest that consolidation with VTD may induce molecular remission in some patients. Ongoing randomized trials by several European study groups are further investigating the use of Bortezomib as consolidation and maintenance therapy. For example, the German DSMM group is investigating the use of Bortezomib as consolidation treatment following high-dose therapy. The phase III GIMEMA trial also includes a randomized consolidation. Following induction treatment with VTD or TD and tandem transplantation, patients are randomized to receive VTD or TD consolidation therapy. In the HOVON 65/GMMG-HD4 trial, there is a comparison of Bortezomib versus Thalidomide maintenance therapy following the initial randomization between PAD or VAD induction.

Can novel agents replace autologous transplantation?

The results of new drug frontline regimens have been obtained mostly in elderly patients or patients with contraindications for ASCT. It is expected that treatment results with new drugs would be similar or even better in younger patients. Therefore, some investigators pointed out that ASCT should no longer be used in frontline therapy. In our view it is a clear recommendation to collect stem cells during the first months of therapy and to perform ASCT frontline until results of randomized trials comparing frontline versus relapse ASCT are available.

In the past, the arguments against ASCT were morbidity and costs. These same arguments can now be used against combinations that include novel agents. The long-term use of these new agents induces severe toxicities (peripheral neuropathy, haematological toxicities, infections, thrombosis) in a relevant percentage of patients. The costs per month are markedly high and some new drugs are used until first progression, accumulating costs and toxicities. The quality of life is an important aspect of cancer treatment. ASCT, as a "single shot" treatment, induces impairment of the quality of life for a short period of time. The strategy of delayed ASCT includes the situation that the feasibility of ASCT related to the age could be a problem for the majority of patients aged between 60 and 65 years at the time of diagnosis. Due to the short follow-up of studies using new drug regimens, the response rate and the VGPR rate are mainly used to justify the claim that these combinations could induce similar results to those observed with ASCT. However, the duration of response appears shorter with these combinations (26 months for MPT, 19 months for MPV, 20 months for RD) than with ASCT (39 months for the IFM 99 trial, more than 5 years for the Thalidomide arm of Total Therapy 2). Results with combinations including novel agents are often compared to results achieved in the 1990s with a single ASCT. But the results of ASCT have recently improved especially with the addition of novel agents before, during, and after HDT.

Thus, new high-dose strategies including new drugs (during induction, high-dose regimen, consolidation, and maintenance) can be expected to induce 80% to 90% VGPRs, including 20% true molecular CRs. These results offer new perspectives in the treatment of MM with a reasonable hope of cure.

CONCLUSION

ASCT has dramatically increased the prognosis of myeloma patients up to the age of 70. The ability of novel agents has changed the frontline strategy not only in older patients, but also in younger patients. Post-ASCT Thalidomide prolongs PFS and probably OS. Novel agents prior to ASCT increase the pre- and post-ASCT CR plus VGPR rates. First results of the IFM showed that the higher response rates are associated with prolonged PFS. The combination of novel agents with ASCT induces very high CR rates, results in high-quality responses and prolongs PFS. However, since combinations with novel agents without ASCT also induce high CR rates, it will be important in the near future to design randomized studies comparing the best regimen including early ASCT with the best non-intensive regimen including ASCT at relapse. Current studies in Europe and North America address this question.

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Време високодозне хемиотерапије у ери нових лекова

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КРАТАК САДРЖАЈ

Терапијски приступ болесницима који болују од мултиплог мијелома битно је промењен увођењем нових лекова, као што су талидомид, бортезомиб и леналидомид. Код болесника код којих је погодна аутологна трансплантација матичних ћелија хематопоезе комбинација нових лекова с конвенционалном хемиотерапијом представља индукционе терапијске модалитете. Примена нових индукционих терапијских модалитета значајно је повећала проценат постигнутих комплетних ремисија пре и после примене аутологне трансплантације матичних ћелија хематопоезе с позитивним утицајем на дужину периода до прогресије болести, што је праћено могућностима за даље побољшање које се постиже применом консолидационе терапије или талидомида и леналидомида као терапије одржавања. Овакви резултати нуде нове перспективе у лечењу особа оболелих од мултиплог мијелома с разумљивим охрабрењем за излечење.

Кључне речи: мултипли мијелом; аутологна трансплантација матичних ћелија хематопоезе; нови лекови