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Strategies for the Treatment of Multiple Myeloma in 2013: Moving Toward the Cure

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1. Introduction

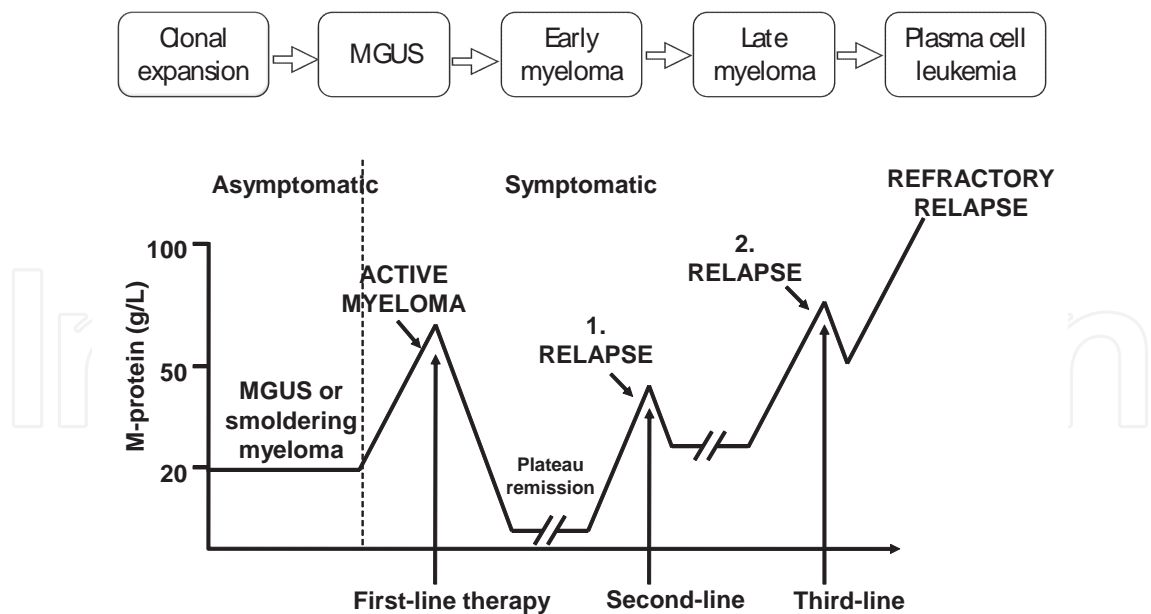
Multiple myeloma (MM) is a hematological disease, and in recent years, overall survival of patients has been significantly increased. Improvement of treatment results is connected not only to the introduction of autologous transplantation of hematopoietic cells into the treatment strategy for younger patients in the 90s but also to the introduction of new beneficial drugs into clinics; in the first decade of this century, bortezomib, thalidomide and lenalidomide were introduced in [1]. These new drugs have repeatedly proven their high treatment efficacy in clinics in all age groups of patients, in primotherapy as well as refractory disease. There are also newer drugs currently under investigation, such as new proteasome inhibitors (carfilzomib, MLN9708 and other peroral proteasome inhibitors) and other immunomodulatory drugs (pomalidomide) with the aim to improve or maintain treatment effects and decrease unfavorable effects in [2]. Using drugs from both these groups together with glucocorticoids and alkylating cytostatics had a major impact on prolonging survival of our patients as previously published. On the other hand, it is clear that use of only one of the new efficient drugs in combination with glucocorticoids and alkylating cytostatics does not lead to a cure in [3-7]. Optimization of dosage in combination with other drugs and the length of treatment have been clarified for thalidomide and bortezomib. Current dosage levels are different from recorded dosages in registration studies which in certain cases led to common or higher level of side effects than is acceptable; these side effects are reduced after optimization. Side effects, especially the long-term ones, may fundamentally influence the quality of life of patients after successful treatment. Nowadays, optimization of thalidomide and bortezomib treatments is almost completed and lenalidomide optimization is currently being processed in [5]. It is logical to think that optimization of efficient drugs is a never ending process that waits for each new efficient drug, for example carfilzomib and pomalidomide in the near future. A

variety of new drugs are being tested in clinical studies at phases I/II. In MM treatment, modern target therapies are being tested, such as monoclonal antibodies, kinase inhibitors or inhibitors of other target molecules connected to one of the signaling pathways important for malignant cells. Although treatment results of this group of drugs failed to reach expectations, we feel that they will produce very promising results in the future. Current treatment strategies will lead to a cure – a topic which is being discussed very seriously. In this chapter, the current state of affairs as well as the potentials of pharmacotherapy in MM will be discussed.

2. Basic scientific data influencing current treatment strategies

Our current treatment strategies originate from a variety of research data that may be shortly described as follows:

- a. Every MM is preceded by a precancerosis called monoclonal gammopathy of undetermined significance (MGUS) in [8]. Individual stages starting from the occurrence of first clonal plasmocyte to MGUS, MM, refractory MM up to plasmocellular leukemia are concurrent; in one individual, they may be described as disease progression changing in time. Many internal and external factors influence the phase when the initial plasmocyte will develop into hematological malignancy requiring therapy (Fig.1).



MGUS, monoclonal gammopathy of undetermined significance

Figure 1. Natural history of multiple myeloma

- b. There is a variety of subtypes of multiple myeloma as this disease is very heterogenous. Thus, MM patients have various prognoses. All currently available classifications (based on ISS, cytogenetics, gene expression profiling, etc.) allow for classification of patients into groups with high, low or sometimes also intermediate risk for long-term survival. Unfortunately, no classification is specific enough to allow for prediction of treatment success and prognosis for each individual patient in [9-11].
- c. Based on the subclonal theory as well as new proofs, it seems probable that there are more clones of plasmocytes present at the time of diagnosis in one patient. Various subclones exist in a dynamic equilibrium, competing for limited resources with alternating dominance of various subclones at different time points. These clones have various characteristics including treatment sensitivity, and their ratio is significantly influenced by the treatment given to patients. It seems that new subclones may originate even during treatment and/or course of the disease in [12,13]. This finding has completely changed our view of efficacy of simple combination treatments with one novel agent. On the other hand, it is in complete harmony with important successes in the treatment including the cure in patients treated with intensive sequences of treatment protocols consisting of most efficient drugs. Drug combinations are essential to overcome resistance and the impact of intra-clonal heterogeneity in [14].
- d. Treatment resistance to a specific drug does not have to be absolute. From the above mentioned subclonal theory, it is obvious that disease resistance to a certain drug in first progression does not have to be resistant to the same drug in the fourth progression. Then, the subclone sensitive to the drug may or may not be prevalent over resistant subclones. In case there are no other treatment options available, it is suitable to test sensitivity to previously used drugs.

3. Treatment strategy and treatment line

When deciding on a treatment, it is necessary to plan a complex treatment – not only anticancer treatment but also supportive treatment; it is important to think about relapse at the time of initial treatment, which drugs to use so that initial treatment does not block further steps in the future. Autologous transplantation is a basic part of treatment wherever possible. Today, treatment strategies use optimal choices of treatment lines, in an individual that should cover 5-7 disease activities within 10 years of treatment if necessary.

4. Newly diagnosed multiple myeloma

Current treatment strategies for newly diagnosed patients are always aiming to reach deepest complete remission - molecular or immunophenotypic in [15,16]. In the first decade of this century, therapeutic regimens with one novel agent as backbone together with glucocorticoids and alkylating cytostatics were used as high standard based on randomized trials (Tab. 1).

Modern protocols of second decade use intensive treatment strategies in the clinical trials called “Multi Agent Sequential Therapy Targeting Different Clones” with at least two novel agents based on the strong evidence of curative potential of such approaches such as Total Therapy trials pioneered by Bart Barlogie in the Little Rock in [14].

MPT	>	MP	Randomized trial 6
MPV	>	MP	Randomized trial 1
MPR - R	>	MP	Randomized trial 1
VMPT - VT	>	MP	Randomized trial 1

M – melfalan, P – prednison, T – thalidomide, V – Velcade (bortezomib); R – Revlimid (lenalidomide)

Table 1. Better PFS on randomized trials with one novel agent based regimen vs. melphalan prednisolon (MP)

1. Induction therapy (2-6 lines of combined therapy) in [17]
2. Myeloablative treatment (1-2 autologous transplantation)
3. Consolidation therapy (3-4 cycles of combined treatment, if possible different from entry induction therapy) in [18,19]
4. Maintenance therapy by lenalidomide and possible combination of drugs should ensure maintenance of remission due to probable immunomodulatory effect in [20,21].

A similar course without myeloablative regimen but with extension of the induction phase of therapy should be evaluated for seniors not indicated for a myeloablative regimen. Unfortunately, in this group of patients, proof of curability is still anecdotal; treatment is less intensive and more modified based on status of the patient. It is important to treat the patient and not the disease. Adequate intensity of therapies in fragile patients is one of the more important aspects for a final positive outcome (Tab. 2) in [22]. Novel combinative fully peroral regimens with two novel agents will further improve prognosis in patients not indicated for myeloablative treatment.

5. Relapse of multiple myeloma

Aims of treatment for patients with relapsed/progressed disease are more limited. Key targets of intensive therapeutic strategies regarding the first and second relapse should be to make the disease chronic again for several years. Balance between efficacy and toxicity as well as long-term toxicity (peripheral polyneuropathy) are main issues in this setting in [23]. Re-

Agent	Dose level 0	Dose level -1	Dose level -2
Dexamethasone	40 mg/d d 1,8,15,22 / 4 wk	20 mg/d d 1,8,15,22 / 4 wk	10 mg/d d 1,8,15,22 / 4 wk
Melphalan	0.25 mg/kg d 1-4 / 4-6 wks	0.18 mg/kg d 1-4 / 4-6 wks	0.13 mg/kg d 1-4 / 4-6 wks
Prednisone	50 mg qod	25 mg qod	12.5 mg qod
Cyclophosphamide	100 mg/d d 1-21 / 4 wks	50 mg/d d 1-21 / 4 wks	50 mg qod d 1-21 / 4 wks
Bortezomib	1.3 mg/m ² twice/wk d 1,4,8,11 / 3 wks	1.3 mg/m ² once/wk d 1,8,15,22 / 5 wks	1.0 mg/m ² once/wk d 1,8,15,22 / 5 wks
Thalidomide	100 mg/d	50 mg/d	50 mg qod
Lenalidomide	25 mg/d d 1-21 / 4 wks	15 mg/d d 1-21 / 4 wks	10 mg/d d 1-21 / 4 wks

Wk, week; d, day; qod, every other day

Adopted from Palumbo & Anderson, New Engl J Med 2011

Table 2. Dose reductions algorithm for frail patients

transplantation is always one of the most effective treatment options during the relapse setting and can be very safely used based on the individual history of the patient in [24]. There is a reduced chance to achieve complete remission if compared to first line therapy. However, combinative regimens using two novel agents (carfilzomib or bortezomib with lenalidomide or thalidomide) are able to induce even higher proportions of remission including complete remission than older types of therapy without the use of immunomodulatory drugs and proteasome inhibitors in newly diagnosed patients (personal experience with lenalidomide and carfilzomib). Generalized benefits for patients in further relapses from a similar number of treatment cycles using one novel agent (IMiD or proteasome inhibitor) is in median at least 1 year in [25]. Thus, the main benefit is not due to overcoming the natural course of the disease but rather to the possibility of using other novel agents in the next relapse. In the advanced disease stage, the treatment is very individualized and reaches a state of stability for a longer period of time (> 6 months) is considered to be acceptable treatment outcome. Long term survival of more than 10 years is currently reached for more than one third of multiple myeloma patients; this has been achieved due to new efficient drugs that can be offered to patients in relapse. It is important to create long-term treatment strategies so that the patient is offered efficient treatment even in third, fourth and further relapses of the disease. The patients who have relapsed after at least two new drugs have a very poor outcome if no other new drug is available, and they should receive the best palliative care in [26].

6. Drugs available for intensive treatments

It is necessary to note that novel agents, immunomodulatory drugs (thalidomide, lenalidomide, pomalidomide) and proteasome inhibitors (bortezomib, carfilzomib), are key players currently used in therapeutical protocols and/or in the clinical trials. The 'old' drugs, such as alkylating cytostatics and glucocorticoids, still belong to the most effective group of drugs in multiple myeloma. These old drugs are used in most treatment protocols. The therapeutic strategy in newly diagnosed patients is described in details in another chapter (Induction Therapy in Multiple Myeloma). The same drugs could be used in a relapse setting depending on the components of initial therapy, efficacy and toxicity of the initial therapy, patient status and circumstances of relapse (age, performance status, glucose metabolism, aggressive vs non-aggressive relapse, bone marrow reserve, renal function impairment, pre-existing peripheral neuropathy and quality of life considerations).

7. Drugs available for the maintenance part of treatment regimen

Decade after decade, there is a change in opinion about benefits of maintenance therapy. While conventional cytostatics and glucocorticoids were used because of lack of any other option, the era of interferon alpha ended with the introduction of immunomodulatory drugs. It is also true that worldwide, interferon alpha had never been accepted as routine maintenance therapy because of its comparatively high toxicity as well as minimal benefit for the unclassified subgroup of patients in [28].

8. Immunomodulatory drugs (IMiDs)

Meta-analysis of randomized clinical studies of phase III with thalidomide as maintenance therapy confirms the benefits of use after autologous transplantation. Statistically significant increase of PFS in six studies and overall survival prolongation in three studies were noted. On the other hand, only one third of patients tolerated thalidomide maintenance therapy for more than a year. At this point, when there are less toxic drugs available for maintenance therapy, thalidomide is recommended as a part of short-term intensive consolidation therapies in [29,28,30].

Lenalidomide was tested in two independent randomized clinical trials of phase III as maintenance treatment after autologous transplantation. Both these trials, CALGB 100104 and IFM 2005-02, demonstrated benefit from lenalidomide compared to placebo, which showed a major decrease in risk of progression by 60% in [21] and an improvement of three-year PFS in the group with lenalidomide (61% vs. 34%) in [20]. Based on new analyses (follow-up of 28 months), there was a statistically significant improvement in overall survival in Len/Dex treated groups of patients in comparison to the placebo treated group of patients, regardless of short follow-ups in [21]. Its role in maintenance therapy is highlighted by improved results

when RMP-R treatment is used with maintenance therapy compared to RMP without maintenance therapy in a study of seniors MM-015 in [31]. RMP-R treatment ensured one of the longest median of PFS (31 months). Maintenance therapy of lenalidomide was generally well tolerated with no signs of cumulative toxicity as in the case of thalidomide. Although the occurrence of secondary malignancies after lenalidomide treatment was increased, the risk of disease progression or death by MM overcame this risk in [5]. Despite superb results of maintenance therapy by lenalidomide, it is not yet approved for maintenance therapy till the end of the year 2012 mainly due to safety reasons, although long-term results are also limited.

9. Inhibitors of proteasomes

In the study GEM/Pethema, patients were induced by VMP (bortezomib, melphalan, prednisolon) or VTP (bortezomib, thalidomid, prednisolon) and randomized for maintenance treatment (VT or VP) for 3 years. Maintenance treatment with bortezomib increased IF-CR from 24% to 42% in [32]. Maintenance treatment with bortezomib was better after autologous transplantation in comparison to thalidomide (PFS 28 vs. 35 months; $p=0.002$), and overall survival benefit was seen not only for the whole group ($p=0.049$) but also for high risk patients in [33]. So far, there is not enough information about maintenance therapy with bortezomib although the data are promising. The change in the route of bortezomib administration from intravenous to subcutaneous significantly reduced toxicity, mainly peripheral polyneuropathy in [34]. Thus, long-term use of bortezomib will be more suitable for patients starting at the end of the year 2012. Moreover, novel proteasome inhibitors that undergo clinical trials have limited toxicity and per oral route of administration that further increased their potential for maintenance therapy in [35].

10. Curability of available treatment options

Multiple myeloma is curable if an intensive combination regime is used upfront. Long-term complete remission becomes a more important factor than reaching complete remission. Complete remission that lasts more than three years is the first milestone on the road towards curability in [36]. It is necessary to accentuate that in the light of current knowledge and long-term experience with intensive regimens, the possibility of curing MM patients is being discussed from the end of 2011 in [37]. The first report, at the time very provocative, was presented at ASH in 2009 suggesting the possibility of a cure in 2009 in [29]. This was a major breakthrough in the observation of this malignant disease.

Which MM patients have a chance of a cure and what is that chance? Curability depends on reaching a deep and constant complete remission which is most probable and possible in MM patients with a favorable prognosis suitable for autologous transplantation. Of which are treated by an intensive combination treatment composed of the most effectively available drugs. These drugs are set into a complex block of entry induction therapy followed by

maintenance therapy. Curability is possible only in patients with a low-risk based on gene expression profiles and cytogenetics based on experience from Total Therapy 3 treatment protocols in [30]. It is important to realize how many patients really have this chance. Of all MM patients, about 40% are involved in intensive treatments. Out of these patients, about 80% are low risk which means about 32% of entry number. To simplify the calculation, about 75% of these patients reach complete remission (24% of entry numbers), and up to 85-90% of these patients reach long-term complete remission (21% of entry numbers) with a chance of curability at about 50-60% (10-12% of entry numbers) in [29,36,30]. Thus, based on available data, a qualified estimate would suggest that a chance for cure is possible for 10% of MM patients and 25% of patients who are able to undergo intensive treatments including myeloablation. These results changed natural course of the disease (Fig.2); moreover, they were impossible 20 years ago.

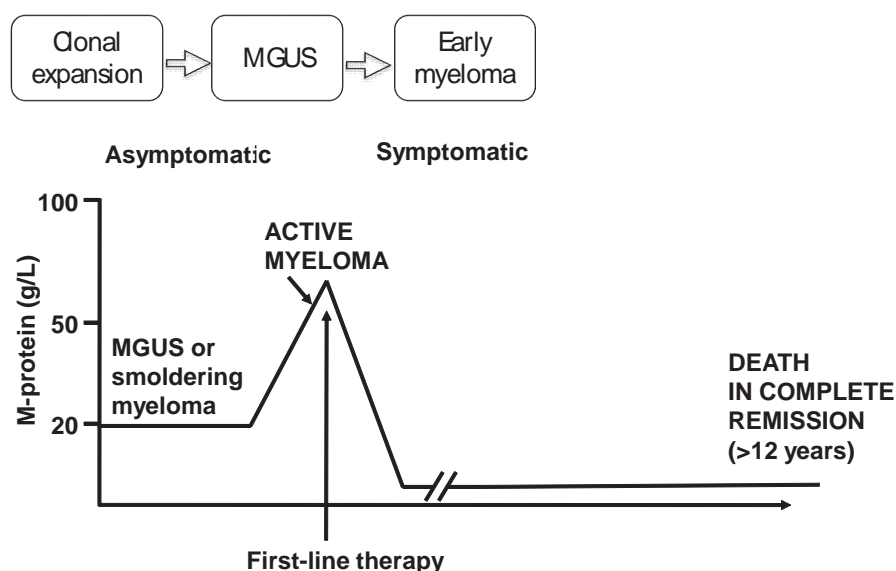


Figure 2. Natural history of multiple myeloma can be changed

11. Summary

In 2012, we can announce MM to be a curable disease under favorable prognostic conditions at the time of diagnosis and using intensive therapy in about 10% of MM patients. Relapsed MM or disease progression is not curable using current treatment options with the exception of allogeneic transplants in some cases. Due to highly efficient drugs, especially proteasome inhibitors and immunomodulatory drugs, our current treatment options are such that we can

modulate another 5-6 active parts of the disease and offer long-term survival of more than 10 years to more than 1/3 of the patients.

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