



Induction Therapy in Multiple Myeloma

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In most hematologic malignancies the role of induction treatment is to achieve complete remission (CR). In multiple myeloma this has been possible only with the introduction of high-dose therapy plus autologous stem-cell transplantation (ASCT). In the context of ASCT there is a statistical relationship between CR or very good partial remission (VGPR) achievement and progression-free survival or overall survival. High-dose therapy consists of 3 to 6 courses of a dexamethasone alone or combined with vincristine-adriamycin (VAD) to reduce the tumor burden and the plasma cell infiltration followed by 1 or 2 courses of high-dose melphalan plus ASCT. This treatment induces 20% to 40% CR and 40% to 55% CR/VGPR. The introduction of novel agents in the induction treatment is changing this scenario. The combinations

of dexamethasone with thalidomide, bortezomib or lenalidomide increase the CR/VGPR rates compared to dexamethasone or VAD. Triple combinations are currently being evaluated, but preliminary results with not more than 3 or 4 cycles show post-ASCT CR/VGPR rates of 60% to 75%

In elderly patients who are not candidates for ASCT, combinations of melphalan-prednisone with a novel agent (thalidomide, bortezomib or lenalidomide) yield CR/VGPR rates that are quite comparable to those achieved in younger patients with ASCT. Prolonged treatment with the combination of lenalidomide plus dexamethasone can be administered safely and appears to induce very high (up to 70%) CR/VGPR rates as well.

Introduction

The role of induction therapy is to induce remission. In acute leukemias the first condition to obtain long-term survival is to achieve complete remission (CR) after induction treatment. In multiple myeloma (MM), CR achievement has long been such a rare event that it was not the objective of the initial treatment and that the term “induction treatment” was almost not used.

The Impact of CR Achievement in MM

With conventional-dose chemotherapy, it was not possible to demonstrate the benefit of CR since CR was achieved in less than 5% of cases with melphalan-prednisone and in less than 10% in dexamethasone-based regimens such as VAD. The prognostic impact of CR was only discussed after the introduction of high-dose therapy plus autologous stem cell transplantation (ASCT). The IFM 90 randomized trial was the first to demonstrate the superiority of high-dose therapy compared to conventional chemotherapy in terms of response rate, progression-free survival (PFS) and overall survival (OS).¹ These results were fully confirmed by the larger trial published by the British Medical Research Council 7 years later.² As a consequence, until now, ASCT is considered standard of care as part of frontline therapy at least in younger patients (up to 65 years of age) with a normal renal function.³

Another important finding from the IFM 90 trial was that, as in many other hematologic malignancies, CR achievement is a major prognostic factor. Patients achieving CR (disappearance of the serum and/or urine M-com-

ponent) or at least very good partial remission (VGPR), defined by a 90% reduction of the serum M-component, had a significantly longer OS than patients achieving only partial remission (PR). The prognostic impact of CR achievement has been confirmed by a number of studies, and a recent metaanalysis has shown that, in the context of ASCT, maximum response is associated with significantly longer PFS.⁴ This prognostic impact of CR or at least VGPR achievement induced two important consequences

New definitions of response to treatment criteria in MM

The first new classification was proposed by an EBMT working group in 1988, which introduced the concept of CR defined by normal bone marrow and negative blood/urine immunofixation, confirmed 6 weeks later.⁵ More recently the International Myeloma Working Group proposed revised uniform criteria.⁶ This classification system introduces the concept of stringent CR (CR plus normal free light chain assay and normal bone marrow by immunochemistry or flow cytometry) and includes VGPR, defined either by a normal electrophoresis but positive immunofixation or by 90% reduction of the M-component.

New objectives of treatment

One of the objectives of subsequent clinical trials was to increase the CR or CR/VGPR rates. During 15 years, the best way to achieve CR was high-dose therapy plus ASCT.

The introduction of novel agents is changing the treatment paradigm in MM. With thalidomide, bortezomib or lenalidomide combined with either dexamethasone or with

conventional chemotherapy, it is now possible to achieve CR rates that are comparable to those achieved with high dose therapy plus ASCT

Induction Treatment in Younger Patients

In the first studies on ASCT, CR or CR/VGPR was mostly achieved only after high-dose therapy. Therefore, induction treatment (meaning “treatment aimed at inducing CR”) was the combination of a limited number (3 to 6) of conventional chemotherapy courses followed by high-dose melphalan plus ASCT. Conventional chemotherapy was given with the objective of reducing tumor burden and facilitating hematopoietic stem cell collection. With this approach, the final CR and CR/VGPR rates were in the range of 20% to 30% and 40% to 45% respectively. Since melphalan was considered too toxic for stem cells, dexamethasone-based regimens were preferred prior ASCT. However, the CR rates achieved with these regimens prior to ASCT were low (less than 10%)

The first improvement came from further dose-intensification, mainly with double ASCT.⁷ With this more aggressive approach CR and CR/VGPR rates increased to 30% to 45% and 45% to 55%, respectively. In currently published randomized trials comparing single and double ASCT, better tumor burden reduction by the induction treatment including double ASCT translated into a significantly longer PFS.⁸⁻¹⁰

More recently, novel agents (thalidomide, bortezomib and lenalidomide) have changed frontline therapy in the context of ASCT as well. They can be used both before and after ASCT. The objective of giving novel agents prior to ASCT is to increase the CR or CR/VGPR rate both before and after ASCT without increasing toxicity.

Thalidomide-based regimens prior to ASCT

The first novel agent tested as initial treatment to reduce tumor burden prior ASCT was thalidomide combined with dexamethasone (Thal/Dex). As thalidomide is not myelotoxic, the quality of stem cell collection with this combination was only slightly reduced compared with VAD.¹¹ Studies comparing Thal/Dex and dexamethasone-based regimens are in **Table 1**.¹²⁻¹⁴ Overall, Thal/dex regimens yielded superior response rates¹²⁻¹³ or VGPR rates.¹⁴ However, after 4 courses of Thal/Dex, the CR rate remained low. More importantly, the post-ASCT rate was not improved compared with VAD, due to the major impact of high-dose melphalan.¹⁴ Moreover, this regimen induced a high incidence of deep-vein thrombosis, justifying prophylactic anti-coagulant treatment. Therefore, Thal/Dex cannot be considered a major improvement compared with dexamethasone alone or with VAD as initial treatment prior to ASCT.

The addition of a third agent to Thal/Dex, either cyclophosphamide or adriamycin appears to improve the CR/VGPR compared with conventional VAD-based regimens, not only prior but also after ASCT^{15,16} (**Table 1**).

Bortezomib-based regimens prior to ASCT

Following encouraging results of Phase II studies testing the combination of bortezomib plus dexamethasone (Vel/Dex),¹⁷⁻¹⁹ the IFM has completed a randomized Phase III study comparing 4 courses of VAD and of Vel/Dex prior to ASCT in 482 patients up to the age of 65.²⁰ Results are in **Table 2**. Compared to VAD, Vel/Dex significantly improved the response rate and the CR/VGPR rate not only before but also after ASCT. The incidence of adverse events was comparable with VAD and with Vel/Dex, but the incidence of grade 2/3 peripheral neuropathy was superior in the Vel/

Table 1. Thalidomide-based induction regimens prior to ASCT: results of comparative studies.

Author	Rajkumar ¹²	Cavo ¹³	Macro ¹⁴	Lokhorst ¹⁵	Morgan ¹⁶
Treatment	TD vs D 4 cycles	TD vs VAD 4 months	TD vs VAD 4 months	TD vs VAD 3 cycles	TCD vs CVAD NA
Number of patients	201	200	204	402	251
Results prior to ASCT, %					
CR	4 vs 0	10 vs 8	12.5	4 vs 2	20 vs 12
> VGPR	—	19 vs 14	35 vs 17	33 vs 15	38 vs 26
> PR	69 vs 52	76 vs 52	—	72 vs 54	96 vs 83
Results after ASCT, %					
CR	—	—	—	16 vs 11	58 vs 41
> VGPR	—	—	44 vs 42	49 vs 32	67 vs 43
> PR	—	—	—	79 vs 76	99 vs 96
DVT	17 vs 3	15 vs 2	23 vs 7.5	8 vs 4*	NA

* Low Molecular Weight Heparin prophylaxis

Abbreviations: NA, not available; DVT, deep vein thrombosis; TD, thalidomide/dexamethasone; D, dexamethasone; VAD, vincristine/adriamycin/dexamethasone; TCD, thalidomide/cyclophosphamide/dexamethasone; CVAD, cyclophosphamide/vincristine/adriamycin/dexamethasone; CR, complete response; VGPR, very good partial response; PR, partial response

Table 2. Bortezomib-based induction treatment prior to autologous stem cell transplantation (ASCT): results of randomized studies.

Author	Harousseau ²⁰	Cavo ³¹
Treatment	VD vs VAD (4 cycles)	VTD vs TD (3 cycles)
Number of patients	482	256
Results prior to ASCT, %		
CR + n-CR	21 vs 8	36 vs 9
> VGPR	47 vs 19	60 vs 27
> PR	80 vs 63	93 vs 80
CR + n-CR in patients with del(13)	26 vs 9	43 vs 4
Results after ASCT, %		
CR + n-CR	35 vs 24	57 vs 28
> VGPR	62 vs 42	77 vs 54
Peripheral neuropathy grade 3, %	6	7

Abbreviations: VD, vincristine, dexamethasone; VAD, vincristine, doxorubicin, dexamethasone; VTD, thalidomide, dexamethasone, bortezomib; TD, thalidomide, dexamethasone; CR, complete response; n-CR, near CR; VGPR, very good partial response; PR, partial response

Dex arm. After priming with granulocyte colony-stimulating factor (G-CSF) alone, the quantity of CD34⁺ cells collected was > 2.109 in 97% of patients. Therefore Vel/Dex is a new initial treatment prior to ASCT that is well tolerated and more effective than VAD. This regimen could be considered the standard of care to which other regimens should be compared and the backbone of more complex combinations.

As with Thal/Dex, the addition of a third agent has been tested in small Phase II studies²¹⁻²² and a large randomized trial is comparing VAD and the combination of Vel/Dex plus adriamycin.

Lenalidomide-based regimens prior to ASCT

The experience with lenalidomide is currently more limited. A small pilot study of lenalidomide plus dexamethasone (Len/Dex) in newly diagnosed patients showed an overall response rate of 91% with 56% CR/VGPR.²³ A randomized ECOG trial comparing lenalidomide with either high-dose or low-dose dexamethasone showed very high short-term PFS and OS in patients up to 65 years of age.²⁴ However, in both studies, the role of Len/Dex as induction treatment prior to ASCT is unclear since only part of the patients were candidates for ASCT. Moreover lenalidomide induces some degree of myelosuppression and recent publications raised concerns as regards the impact of this agent on peripheral blood stem-cell collection with G-CSF alone.²⁵⁻²⁷ Mobilization with cyclophosphamide plus G-CSF appears to overcome this negative impact of lenalidomide on stem cell collection.^{28,29} More studies in the field of ASCT are needed to evaluate the efficacy/toxicity ratio of this promising combination

Combination of novel agents prior to ASCT

Since bortezomib and IMiDs (thalidomide and lenalidomide) have different mode of actions and different toxicity profiles it appeared logical to combine them in order to increase efficacy. The first combination to be tested was Thal/Dex plus bortezomib (VTD). Although thalidomide and bortezomib may both induce peripheral neuropathy, it was hoped that, with a short treatment, the risk of neurological complications could be low and that the efficacy could be increased. After encouraging results from a pilot study performed by the Houston group,³⁰ the Italian cooperative group Gimema started a randomized comparison of Thal/Dex and VTD as initial treatment prior to ASCT.³¹ Preliminary results are in **Table 2**. VTD combination was clearly superior to Thal/Dex and yielded impressive CR/VGPR rates of 60% and 77%, respectively, prior to and after ASCT

Since lenalidomide does not induce peripheral neuropathy it could be used in place of thalidomide (VRD combination). Preliminary results of this combination in newly diagnosed patients are impressive as well, with a response rate of almost 100%.²⁹

Finally, the Arkansas group has used a short-term initial treatment combining VTD and chemotherapy (VDTPACE regimen) with the objective of obtaining a high response rate with minimal toxicity.³²

Questions currently addressed in younger patients

Available results clearly show that novel agents in the initial treatment prior to ASCT may improve not only the response rate prior to ASCT but also the CR/VGPR rate after ASCT. Vel/Dex appears to be superior to Thal/Dex in terms of CR/VGPR rates, although this has not been shown by a randomized study. In particular, with Vel/Dex combinations the CR rate is not different in patients with poor-risk cytogenetics (**Table 2**). The addition of a third agent could further improve results and the combination of two novel agents as in the VTD regimen appears to be very effective. However, it is too early to determine whether this better tumor reduction after induction treatment with novel agents will translate into a longer PFS and OS.

Moreover, this better efficacy of initial treatments will help to answer the question of the impact of achieving CR prior to ASCT. Until now it has not been possible to provide a clear answer to this question since CR rate with conventional chemotherapy prior to ASCT was so low. If patients achieving CR/VGPR prior to ASCT have a better outcome than patients achieving CR after ASCT, ASCT could be considered as a consolidation and the initial treatment would become the Induction Treatment (as in AML for instance).

Is it possible to further increase CR/VGPR rate by the addition of novel agents after ASCT? Three randomized studies have evaluated the impact of thalidomide given after ASCT as maintenance treatment³³⁻³⁵ and in a fourth

study, thalidomide was given from the initiation of treatment until relapse or adverse event.³⁶ All four trials show a significant PFS and OS advantage but also an increase in the CR/VGPR rate in the thalidomide arm. In total therapy 3, the near-CR rate increased from 45% at 6 months to 83% at 24 months after double ASCT and consolidation with novel agents.³² Ongoing trials are evaluating bortezomib and lenalidomide as post-ASCT maintenance. Therefore, when more mature data are available, the standard intensive frontline therapy for younger patients could become induction with novel agents, ASCT as consolidation and maintenance with novel agents

Induction Treatment in Elderly Patients

For more than four decades the standard of care for frontline therapy in elderly patients has been melphalan-prednisone (MP). This regimen could not induce more than 5% CR.

The first improvement came from the addition of thalidomide to MP. Two randomized studies comparing MP and MP plus thalidomide (MPT) have been published, one from Italy and one from the IFM.^{37,38} The results are summarized in **Table 3**. In both studies, MPT was superior to MP in terms of response rate, CR or CR/VGPR rates and PFS. In the IFM study OS was also significantly longer in the MPT arm, which was not the case in the Italian study due to a shorter OS after relapse in the MPT arm. Three other randomized studies have not yet been published. Another IFM study in patients aged over 75 and a Dutch study confirm the superiority of MPT,^{39,40} while a study from the Nordic group is negative.⁴¹

The combination of bortezomib with MP (MPV) has been tested in Phase I/II study by the Spanish group.⁴² The outstanding CR rate (32% with negative immunofixation plus 11% near CR with positive immunofixation) was the rationale for a large randomized trial comparing MP and MPV⁴³ (**Table 3**). This trial confirmed that MPV can yield impressive CR and CR/VGPR rates (35% and 45%, respectively). Although the follow-up is still short, PFS and OS are superior in the MPV arm.

This high CR rate could be due partly to the efficacy of bortezomib in patients with poor-risk cytogenetics, including del 13 and t(4;14).

Preliminary experience of the combination of MP plus

lenalidomide (MPR) has been published by the Turin group.⁴⁴ Again, results were considered good enough to justify a large randomized Phase III study, which is currently comparing MP and MPR.

The Len/Dex combination has also been tested in patients who were not candidates to ASCT. In the randomized ECOG trial, the overall CR/VGPR rates were 52% with high-dose dexamethasone and 42% with low-dose dexamethasone.²⁴

Questions currently being addressed in elderly patients

What is the best induction treatment in elderly patients? The question is not only to determine which of the novel agents offers the best efficacy/toxicity ratio when combined to MP but also to know whether melphalan is necessary in the induction treatment. The combination of two novel agents (VRD regimen) looks very promising.²⁹

What is the optimal duration of induction treatment with novel agents? Two different strategies have been used in the MP versus MPT or MPV studies, either a fixed number of cycles or treatment until relapse or side effects. These two strategies are being compared in an ongoing randomized trial with MPR

Is maintenance treatment necessary once maximal result has been achieved? Until now no randomized study has evaluated the impact of maintenance therapy after remission induction with novel agents.

Table 3. Novel agents in front-line therapy for elderly patients: results of randomized studies.

Author	Palumbo ³⁷	Facon ³⁸	San Miguel ⁴³	Rajkumar ²⁴
Treatment	MPT vs MP	MPT vs MP	MPV vs MP	RD vs Rd
Duration of planned treatment	6 mo + T until relapse in MPT arm	18 mo	54 wk	NA
Median duration of treatment	8 m (T)	11 m (T)	46 w (V)	4 m vs 6 m
Number of patients	255	321	682	445
Response rate, %				
CR	15.5 vs 2.5	13 vs 2	35 vs 5	4 vs 2*
>VGPR	36.5 vs 11	47 vs 7	45 vs 10	52 vs 42
>PR	76 vs 47.6	76 vs 35	82 vs 50	82 vs 71
2-year PFS, %	54 vs 26	65 vs 35	45 vs 25	40 vs 40
Thrombosis + embolism, %	12 vs 2	12 vs 4	1 vs 1	25 vs 9
Peripheral neuropathy, grade 3, %	8 vs 1	6 vs 9	13 vs 0	2 vs 1

*CR may be underestimated since bone marrow evaluation was not always performed. Abbreviations: MP, melphalan plus prednisone; MPT, MP plus thalidomide; MPV, MP plus bortezomib; RD, lenalidomide plus high-dose dexamethasone; Rd, lenalidomide plus low-dose dexamethasone; T, thalidomide; V, bortezomib; CR, complete response; VGPR, very good partial response; PR, partial response; PFS, progression-free survival

Comparison of intensive and Non-Intensive Induction Treatments

It is currently difficult to compare the intensive and the non-intensive induction treatments for several reasons:

- Intensive treatment has been used in younger patients and non-intensive treatment mostly in older patients (over 65 years).
- Follow-up is still short for a number of studies with novel agents.
- Duration of treatments are different.
- Until now no randomized study has compared the two approaches.

However, despite the dramatic improvement of non-intensive induction regimens obtained by the addition of novel agents to MP or to dexamethasone, available results remain in favor of intensive induction regimens, as shown in **Table 4**. Intensive induction regimens remain superior in terms of CR/VGPR rates. With MPT, MPV or Len/Dex, CR/VGPR rates of 35% to 45% can be achieved, which is quite comparable to what was achieved after single ASCT. However, double ASCT increased the CR/VGPR rates to 45% to 55%, and the introduction of novel agents further improves these results (from 60% with VD or TCD to almost 80% with VTD).

In terms of PFS, there is no apparent difference between novel agents without ASCT and single ASCT without novel agents (24 to 30 months). However after double ASCT without novel agents, PFS is apparently better (>30 months). Although the follow-up of studies with novel agents prior to ASCT is still too short, one can hope that the better tumor reduction after this combined induction treatment will translate in a longer PFS. Longer follow-up is needed before confirming that this approach is a new standard of care.

Moreover, results of intensive induction are further improved by the use of novel agents after ASCT. With thalidomide maintenance after intensive induction regimen, median PFS may be longer than 4 years.³³⁻³⁵ When novel agents are used both before and after ASCT, impressive preliminary results are obtained (2-year event-free survival and OS 84% and 87%, respectively).⁴⁵ On the other hand, while the interest of maintenance therapy after non-intensive induction regimens has not yet been proved, prolonged treatment with Len/Dex may induce outstanding VGPR and 2-year PFS as well.⁴⁶ Therefore, a randomized comparison of novel agents versus novel agents plus ASCT is necessary, especially since salvage treatment including ASCT at relapse could be superior in a non-intensive

induction regimen. Another objective of such a randomized trial would be to try and define which patients actually need early ASCT in the era of novel therapies.

Is Complete Remission the Objective of Induction Therapy in All Situations?

Until now, the prognostic impact of CR achievement has been shown mostly in the context of high-dose therapy since CR was too rare with conventional chemotherapy. Since novel agents in combination with MP or with dexamethasone induce high CR rates, it should be possible to confirm the impact of CR in this setting as well. In randomized studies comparing MP and MP plus either thalidomide or bortezomib, the improved PFS observed with the addition of a novel agent was always associated with an increased CR/VGPR rate.

However, recent studies suggested that the prognostic impact of CR achievement might not exist in all types of MM. For instance, patients with a pre-existing monoclonal gammopathy of unknown significance (MGUS) could have a good prognosis even if they don't achieve CR.⁴⁷ On the other hand, patients with poor-prognostic features such as t(4;14) can achieve CR but still relapse early.⁴⁸ The Arkansas group has recently stated that the benefit of CR achievement is significant only in the small subgroup of patients (13%) with a poor prognosis as defined by gene-expression profile.⁴⁹ Therefore, the impact of CR probably depends on the magnitude of response, which is in relation not only with the efficacy of treatment but also with the prognostic subtype of MM. In patients with less aggressive MM, achievement of VGPR could be a sufficient objective.

Finally, the combination of effective induction treatment and of post-ASCT consolidation/maintenance therapy may induce cytogenetic or even molecular remissions that appear to be critical for long-term survival.^{50,51} Combined modality approaches (with the addition of several active agents) will further improve the quality of response, which will probably justify a new definition of response criteria, as this is already the case in acute and chronic leukemias.

Table 4. Comparison of intensive and non-intensive induction treatments (in the absence of maintenance therapy): results of randomized studies.

	Conventional CT + single ASCT	Conventional CT + double ASCT	Novel agents + ASCT	Novel agents without ASCT
References	Attal ^{1,8} Child ² Harousseau ³	Attal ⁸ Cavo ⁹ Barlogie ³⁶	Harousseau ²⁰ Morgan ¹⁶ Cavo ³¹	Palumbo ³⁷ Facon ³⁸ San Miguel ⁴³
CR rate, %	20-40	30-45	35-55	15-35
> VGPR rate, %	35-45	45-55	60-80	35-45
PFS, mo	median 25-30	median 30-40	?	24-28

Abbreviations: CT, computed tomography; ASCT, autologous stem cell transplantation; CR, complete response; VGPR, very good partial response

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