Consolidation in multiple myeloma – current status and perspectives

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Although multiple myeloma (MM) is still considered an incurable disease, the treatment philosophy is changing due to the introduction of novel agents. Standard treatment consists of an induction phase and autologous stem cell transplantation in patients under 65–70 years. Prolonged treatment (consolidation and/or maintenance) is being introduced in many countries. We present a review of clinical trials dedicated to consolidation treatment in multiple myeloma. Bortezomib, lenalidomide and carfilzomib in different combinations were tested in the trials mentioned below. Although they did not prolong overall survival, the data are very promising. Three very important large clinical trials are still in progress. The results might help to establish the actual value of consolidation treatment.

Key words: myeloma, consolidation, bortezomib, lenalidomide, ASCT.

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Introduction

Nowadays, patients with multiple myeloma (MM) live twice as long than they did twenty years ago. New drugs have prolonged overall survival (OS) and progression-free survival (PFS) and improved the quality of patient's life (QoL). Although MM is still considered an incurable disease, the treatment philosophy has changed due to the introduction of novel agents. It is also proved that the depth of response determines the duration of PFS and OS [1].

Researchers have shown that the pathological plasmocyte population in a specific patient is not monomorphic. According to the concept of clonal tides, one of the competing subclones becomes dominant, but during the treatment some of the other subclones might become prevalent [2].

The induction should lead at least to partial remission (PR). Then in relatively young patients (65–70 years) autologous stem cell transplantation (ASCT) is conducted. ASCT is still considered the standard of care for frontline therapy in myeloma patients. For the last few years attempts have been made to deepen the response by consolidation and/or maintenance treatment. According to its definition, consolidation therapy is a short therapy carried out to improve the response quality, while maintenance treatment (which should last much longer) is mainly taken up to prolong the effects achieved before. In the light of reports on clonal heterogeneity in the myeloma population, consolidation treatment has become a very interesting prospect.

Several years ago, consolidation therapy after ASCT could consist of further ASCT [4]. The double ASCT strategy was proposed to patients achieving less than a very good partial response (VGPR) after the first procedure [5]. Still the procedure is carried out in selected patients in some health centres.

Clinical trials review

An Italian trial under the leadership of Marco Ladetto was of key importance though it had few participants. It was one of the first clinical studies to demonstrate the benefits of novel agents used after ASCT. Thirty-nine patients who achieved after ASCT at least very good partial remission (VGPR) were enrolled (2004–2007). Induction treatment included VAD-like regimens; therefore the patients were naïve to novel drugs. Tandem ASCT was carried out in all patients. Consolidation treatment consisted of four VTD (bortezomib, thalidomide, dexamethasone) cycles. In addition to regular evaluation of response, patients with tumour clone specific primers were studied by qualitative nested PCR and RQ-PCR. The immunofixation complete response rate increased from 15% after ASCT to 49% after consolidation. Meanwhile the molecular remission rate rose from 3% after ASCT to 18% after VTD. At the time of publication, in 2010, no patient in complete molecular remission (MR) had relapsed. After a median follow-up of 42 months, median PFS was 60 months and projected OS at 3 years 89% [6].

In 2009 Andrew Spencer presented the result of a phase III randomised study on consolidation treatment with thalidomide and low doses of prednisolone (Tp). Two hundred and sixty-nine patients who achieved at least sta-

bilization of the disease after conventional chemotherapy were enrolled (2002–2005). After the ASCT procedure, 129 patients were randomly assigned to receive prednisolone maintenance therapy and 114 to receive thalidomide plus prednisolone 12-month consolidation, but next prednisolone maintenance. After a median post-randomization follow-up of 3 years, 3-year PFS was 42% in the consolidation group and 23% in the "just maintenance" group ($p < 0.001$). Overall survival rates were 86% in thalidomide patients and 75% in control patients ($p = 0.004$). There was no difference in patients' survival 12 months after progression (79% vs. 77%, $p = 0.237$). Neurological toxicities were more common in the thalidomide arm (11 in 3/4 grade) vs. none in the prednisolone arm [7].

During the 2013 ASH meeting the final analysis of the study was reported [8]. After a median follow-up of 5.4 years, 2 patients per arm were lost from each arm. Five-year PFS was 27% in the thalidomide group vs. 15% in the prednisolone group ($p = 0.005$). Analogously, OS rates in the two groups were 66% vs. 47% ($p = 0.007$). The authors observed that the patients who achieved VGPR or complete response (CR) after ASCT did not benefit from thalidomide consolidation. Moreover, the patients required at least 8 months' exposure to thalidomide to prolong PFS and/or OS ($p < 0.001$). Thalidomide after ASCT did not diminish the ORR (overall response rate) when salvage therapy had to be introduced.

Recently the Nordic Myeloma Study Group (NMSG) published results of their randomized phase 3 trial assessing the efficacy of bortezomib monotherapy as consolidation treatment after ASCT. Three hundred and seventy patients, who had not been exposed to bortezomib, were enrolled three months after single or tandem ASCT. The most common initial treatment was Cy-Dex (cyclophosphamide and high doses of corticosteroids). One hundred and eighty-seven patients received bortezomib consolidation (20 doses). Meanwhile the control group of 183 people was observed. Glucocorticosteroids in the maximum dose of 50 mg of prednisolone per week were allowed. The overall median follow-up time was 38 months. At randomization there was no difference in response rates between the groups: 40% had achieved at least VGPR. The best response during the study was achieved in more-bortezomib treated patients: VGPR 71% vs. 57% ($p < 0.01$). The improvement from partial response (PR) to at least VGPR was shown by 57% in the bortezomib group vs. 36% in the observation group ($p = 0.007$). In the consolidation group PFS was 27 months while it was 20 months in the observation group ($p = 0.005$). After 3 years of follow-up, OS was similar in both groups (≈80). Neuropathy related to bortezomib is a major side effect [9]. Sensory peripheral neuropathy was reported by 57% of patients in the consolidation group vs. 24% in the control group. Sensory neuropathy grade 3 or higher (CTC scale) was observed in 5% of bortezomib treated patients and 1% of controls ($p < 0.04$). There were no other major differences in QoL between the two groups. According to the authors, only the patients who had not achieved at least VGPR after ASCT derived significant benefits from bortezomib consolidation. It is worth mentioning that five-month treatment prolonged PFS by seven months [10].

In 2012, at the ASH meeting, scientists from the IFM trial presented a retrospective analysis on the multidrug consolidation scheme VTd: bortezomib, thalidomide and dexamethasone. In contrast to the Nordic trial, new drugs were used from the beginning of the treatment. The first cohort (#1) of 121 patients was given VTd in induction, then underwent ASCT, and in consolidation they were given the same scheme. The second cohort (#2) of 76 patients (from the IFM-2007-02 trial) was treated with VTd and ASCT without consolidation. The third cohort (#3) of 40 patients received upfront triplet bortezomib based combination (VCd, VRd) and underwent ASCT without consolidation. Median follow-up was 25 months. Overall response rate equal to or higher than partial remission at completion of therapy was identical (#1 vs. #2 vs. #3: 94% vs. 99% vs. 87%). Nevertheless, the CR rate was significantly higher in the consolidation cohort (#1): 53% vs. 36% vs. 35% ($p = 0.0001$). It is significant that after ASCT, CR rates were identical. In patients who received consolidation therapy the incidence rate of relapse was significantly lower: 21% vs. 55% vs. 32.5% ($p = 0.0001$). Median OS or median PFS was not reached at the moment of publication. The safety profile was comparable in all three cohorts [11].

At the ASH 2013 meeting, French scientists presented the results of a study on consolidation with VTd in myeloma patients with PR at completion of induction with VTd [12]. One hundred and twenty-one patients who underwent VTd-ASCT-VTd from 2009 to 2011 were taken into the analysis. Fifty-four patients achieved PR after VTd induction. At completion of consolidation, 33% achieved VGPR and 35% CR. Thirty-five percent of the patients who did not benefit from ASCT (15 patients – still in PR after ASCT) improved response after consolidation. The median time to progression (TTP) was less than 16 months in patients who did not improve their response after consolidation and was not reached in the group that benefited from VTd consolidation. Three-year PFS was 18% in the first group and 58% in the second group. The median OS was reached in neither of the groups. According to the authors, 68% of patients who achieved only PR after VTd induction did benefit from VTd consolidation.

The GIMEMA group conducted a phase 3 randomised prospective study comparing TD (thalidomide, dexamethasone) to VTD (bortezomib, thalidomide, dexamethasone) as consolidation after ASCT. Four hundred and eighty patients were enrolled (2006–2008). The first randomization to TD and VTD groups was carried out before induction treatment.

After the induction, double ASCT was conducted. Thalidomide and dexamethasone were administered from recovery of haematopoiesis until the second transplantation. Regardless of response to transplantation, three months after the second ASCT two consolidation courses were applied (VTD vs. TD).

One hundred and sixty patients in every arm completed the treatment and were included in the analysis. After the consolidation phase, CR rates were 60.6% in VTD patients

Table 1. Post-transplantation consolidation treatment in myeloma patients

Author	*N*	Induction therapy	Consolidation scheme	Comparator	Duration/ No. of cycles	CR rate %: Cons+/–	PFS: Cons+/–	OS %: Cons+/–
Bortezomib based regimens								
Ladetto et al. 2010 [6]	39	VAD-like regimens	VTD	No	4 cycles	49 18-molec.	60 months	3 y OS (projected) 89%
Spencer *et al.* 2009 [7]	269	various "classic" regimens	Tp	prednisone	1 year	CR/VGPR: 63/40	3 y PFS: 42/23%	3 y OS 86/75%
Spencer – final analysis in 2013							5 y PFS: 27/15%	5 y OS: 66/47%
Mellquist *et al.* (NMSG) 2013 [9]	370	non-bortezomib based	bortezomib monotherapy	observation	6 cycles	CR/nCR: 45.1/35%	27/20 months	3 y OS ~80/80%
Leleu (IFM) 2013 retrospective [11]	237	VTd/VTD/ VRD	VTD	TD/ observation	2 cycles	35/21/32		4 y OS 91/90/44%
Cavo *et al.* (GIMEMA) 2012 (2013) [13]	480	VTD/TD	VTD	TD	2 cycles	60.6/46.6	3 y PFS: 60/48%	3 y OS 90/88%
GIMEMA (updated in 2012)							56/42 months	no difference between groups
Carfilzomib based regimens								
Sonneveld 2012 [18]	50	CTD	CTD	–	4	35	1 y PFS 97%	1 y OS 100%

vs. 46.6% in Td patients ($p = 0.012$), whereas after the second ASCT, CR rates were 48.7% vs. 40.4% ($p = 0.131$).

In the VTD cohort median PFS was not reached, whereas in the TD cohort it was 32 months. According to the authors, patients who most benefited from VTD consolidation therapy were those who did not reach CR after ASCT.

The VTD scheme in the consolidation phase was beneficial even in high cytogenetic risk groups (del17p, t(4;14)). No difference of OS was seen between the two groups of patients.

Bortezomib attachment caused higher incidence of adverse effects, but they were usually of mild to moderate grade. In general, neurotoxicity was lower in the consolidation stage than in induction treatment [13].

At ASH 2012, updated results of the GIMEMA trial were announced [14]. After a median follow-up of 52 months, a benefit from incorporation of bortezomib into consolidation was still relevant. In the VTd arm PFS was 56 months, and in the Td arm it was 42 months ($p = 0.001$). Moreover, short-term treatment with bortezomib did not influence the sensitivity of myeloma cells to bortezomib-based salvage therapy.

Terragna examined the molecular response in GIMEMA patients and analysed 67 patients who achieved CR and near CR before consolidation beginning. Forty-three percent of patients from the VTD group and 37.5% from the TD group were PCR negative after the second ASCT. After consolidation treatment (+70 day) minimal residual disease (MRD) negativity was achieved by 67% of VTD patients and 52% of TD patients ($p = 0.05$) [15].

In 2011, French scientists announced updated results of the phase 2 randomised trial IFM-2008 evaluating VRD combination applied in induction as well as in the consolidation phase. Thirty-one patients with PCM *de novo* were recruited. The patients received three 21-day VRD cycles (bortezomib, lenalidomide, dexamethasone), proceeded to ASCT and then received two consolidation cycles (the same schedule as in the induction phase) followed by lenalidomide maintenance. Thirty patients completed the consolidation phase and 20 patients completed maintenance therapy. Consolidation therapy with two cycles of VRD upgraded the response in 26% of patients. Considering the safety profile, the most important toxicities were: grade 2 polyneuropathy (13%), and grade 3/4 neutropenia (17%) [16].

Novel agents besides bortezomib and lenalidomide are being introduced more courageously into the first line treatment [17].

At the ASH 2012 meeting, Sonneveld presented the results of carfilzomib therapy of MM *de novo* trial [18]. The authors reported on 40 patients registered to the first (of three) cohorts. Thirty-nine patients completed 4 CTD courses (carfilzomib, thalidomide, dexamethasone), underwent single ASCT, and in the consolidation phase received 4 CTD cycles with a reduced thalidomide dose (50 mg instead of 200 mg). After ASCT, 63% achieved at least VGPR (25% CR), and after the consolidation phase the VGPR or better response rate was 70% (35% CR). PFS was 97% at 12 months and OS was 100%. No haematological toxicity was observed. Non-haematological side effects

grade 3/4 were: *deep vein thrombosis* (DVT) 10%, skin rash 8% and polyneuropathy 17%.

In 2013, Sonneveld announced at the ASH meeting further data on their study [19]: the patients of the first (50 patients) and second (20 patients) cohort. In cohort II the dose of carfilzomib was escalated from 27 mg/m^2 to 36 mg/m^2 in the same schedule as described above. All the patients underwent ASCT and consolidation treatment. Thirty-nine patients completed the protocol, with 19 still on treatment. The CR/sCR rate (which was 30% after ASCT) increased to 49% after consolidation. The response was similar in standard and poor cytogenetic risk patients (+1q or t(4;14) or del17p). The safety profile was acceptable: non-haematological toxicities in 3 + 4 grades were less than 5% (mainly infections and skin manifestations).

In the United States under *National Cancer Institute (NCI)* patronage consecutive Total Therapy (TT) modifications are being analysed: TT1, TT2, TT3, and TT4. In the TT2 phase III randomized trial (n = 668) consolidation varied and eventually used DPACE (dexamethasone, cisplatin, doxorubicin, cyclophosphamide, etoposide) quarterly for 1 year. In the TT3 phase II trial (n = 303) consolidation used two cycles of VTD-PACE (bortezomib, thalidomide, dexamethasone). All the patients before consolidation underwent tandem ASCT and afterwards received maintenance therapy. The authors of the TT analysis conclude that bortezomib added in the induction and consolidation phase improves the depth of response [20].

In elderly and frail patients who are transplant ineligible, there are also attempts to prolong the therapy including the consolidation phase.

Italian scientists published the results of a phase II trial with lenalidomide as consolidation treatment. Forty-six patients were enrolled in 2008–2009. Median age was 75 years, and more than 30% of them had at least two comorbidities. The patients received 4 RP (lenalidomide, prednisone) cycles as induction treatment followed by 6 MPR (melphalan, lenalidomide, prednisone) consolidation cycles. Afterwards they went to the maintenance phase – RP.

The most frequent adverse events of grade 3–4 were cytopenias, infections and cutaneous reactions. The toxicity of MPR consolidation was significantly lower than standard MPR.

MPR consolidation improved the response in 8 patients (about 25%): in 2 patients from SD to PR, in 5 from PR to VGPR, in 1 from VGPR to CR. Median PFS was 18.4 months and 2-year OS was 80%. PFS and OS rates were similar in standard and high cytogenetic risk patients.

The authors concluded that melphalan dose reduction (50% compared to standard MPR studies) did not influence the response rate but might have affected PFS: 18.4 months with RP-MPR compared with 28–31 months with MPR-R [21].

There are several trials in progress. The most promising among them in the authors' opinion are the following:

A randomized phase III trial under the auspices of the NCI (NCI-2009-00521; NCT00522392) has just ended (VIII 2007 – VIII 2013); the data are being analysed. The subject of the study is a comparison between VRD and VD consolidation. In induction the patients received dexamethasone-based regimens (VAD, TD, RD). Eight cycles of consolidation treatment, VRD vs. VD, were planned. The ASCT procedure was postponed until progression. No data are available yet [22].

The randomised phase III trial IFM/DFCI 2009 (NCT01191060) is still ongoing. This French-American study is designed to evaluate whether ASCT is still the gold standard in frontline MM therapy in the era of novel agents. Seven hundred transplant eligible patients were enrolled in this trial. In arm A the patients receive 2 RVD (lenalidomide, bortezomib, dexamethasone) cycles, then stem cell collection is conducted, and 5 RVD consolidation cycles are given to the patients. In arm B (also after two RVD induction cycles) stem cell collection is conducted but then the patients undergo the ASCT procedure. Lenalidomide maintenance is implemented in both arms. The estimated primary completion date is expected to be in 2018.

A randomised phase III trial under the auspices of BMT and NCI is also still ongoing (BMT CTN 0702; NCT01109004). The goal is to compare the effectiveness of single ASCT with consecutive consolidation treatment to double ASCT. Prior to the first transplant, enrolled patients (750 patients) are randomized to three cohorts. In the first one, patients undergo double ASCT. In the second cohort, after the first ASCT patients receive 4 RVD consolidation cycles. In the third cohort/control group, patients undergo ASCT. All patients proceed to lenalidomide maintenance. The estimated primary completion date is expected to be in 2016.

Discussion

Although the term "consolidation" has been present in myeloma treatment for years, its exact definition is still a matter of debate. It is commonly considered as therapy aimed at improvement of the depth of response after induction and ASCT. By design it should be a relatively short and intense therapy: composed of 2–4 cycles [23]. In Rajkumar's opinion, the distinction between consolidation and maintenance is semantic [24].

So far, there have not been many large randomized trials dedicated to the consolidation phase. Ideally, after uniform induction therapy and ASCT, patients should be randomized into homogeneous groups taking into account the cytogenetic profile.

Satisfactory results achieved with novel drugs encourage scientists to postpone ASCT – there are attempts to shift the procedure to the second line treatment.

In the light of current knowledge on genetic heterogeneity of particular myeloma subclones, we can guess that attaching drugs that were not applied in previous therapy phases might help in eliminating distinct subclones.

So far, there are not sufficient data to establish that consolidation treatment prolongs OS in myeloma patients. As a matter of fact, OS was not the primary endpoint in most of the described trials. Therefore consolidation is not routinely recommended by expert panels [25]. The results of ongoing trials are impatiently awaited to establish the value of consolidation treatment.

Summary

In view of the lack of sufficient evidence of the value of consolidation treatment, it is not recommended in everyday practice. However, more and more clinical centres apply consolidation within multicentre or local clinical trials. It seems that in the near future it might become an element of routine therapy in myeloma. In the authors' opinion, consolidation is a very promising treatment element: a chance to improve the depth of response and to prolong OS. But before this happens, we will have to answer many questions: Who would benefit from consolidation? Can consolidation replace ASCT? How long should consolidation last? What drugs should be used in the consolidation scheme?

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