IRIS AperTO

UNIVERSITÀ DEGLI STUDI DI TORINO

AperTO - Archivio Istituzionale Open Access dell'Università di Torino

Maintenance Therapy for Multiple Myeloma.

This is the author's manuscript

Original Citation:

Availability:

This version is available http://hdl.handle.net/2318/1506217 since

Terms of use:

Open Access

Anyone can freely access the full text of works made available as "Open Access". Works made available under a Creative Commons license can be used according to the terms and conditions of said license. Use of all other works requires consent of the right holder (author or publisher) if not exempted from copyright protection by the applicable law.

(Article begins on next page)

12 October 2024

UNIVERSITÀ DEGLI STUDI DI TORINO

This Accepted Author Manuscript (AAM) is copyrighted and published by Elsevier. It is posted here by agreement between Elsevier and the University of Turin. Changes resulting from the publishing process - such as editing, corrections, structural formatting, and other quality control mechanisms - may not be reflected in this version of the text. The definitive version of the text was subsequently published in [Hematol Oncol Clin North Am. 2014 Oct;28(5):839-859. doi: 10.1016/j.hoc.2014.06.006. Epub 2014 Jul 22.].

You may download, copy and otherwise use the AAM for non-commercial purposes provided that your license is limited by the following restrictions:

(1) You may use this AAM for non-commercial purposes only under the terms of the CC-BY-NC-ND license.

(2) The integrity of the work and identification of the author, copyright owner, and publisher must be preserved in any copy.

(3) You must attribute this AAM in the following format: Creative Commons BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/deed.en), [http://www.hemonc.theclinics.com/article/S0889-8588(14)00080-X/pdf]

Maintenance therapy

Philip McCarthy, MD[1] and Antonio Palumbo, MD[2] *

[1] Blood and Marrow Transplant Program, Roswell Park Cancer Institute, Buffalo, NY, 14263, USA. Email: philip.mccarthy@roswellpark.org; Telephone: 716-845-4074; Fax: 716-845-3272
[2] Myeloma Unit, Division of Hematology, University of Torino, Azienda Ospedaliero-Universitaria Città della Salute e della Scienza di Torino, Via Genova 3, 10126 - Torino, Italy. E-mail: appalumbo@yahoo.com; Telephone.: +39 01 1663 5814; Fax: +39 01 1696 3737

* Corresponding author

Keywords: Multiple myeloma, thalidomide, lenalidomide, bortezomib, transplant-ineligible, transplant-eligibile, maintenance

Key points

- Maintenance therapy with novel agents prolonged remission duration in both transplant-ineligible and transplant-eligible patients with MM.
- The appropriate maintenance strategy should be not only effective but also well tolerated.
- In transplant-ineligible patients, single-agent thalidomide or lenalidomide showed positive results after thalidomide- and lenalidomide-based induction therapies, respectively. Bortezomib in association with thalidomide is also a valid strategy.
- In transplant-eligible patients, single agent thalidomide resulted in improved PFS but was not well tolerated and in high risk cytogenetic patients may lead to inferior survival whereas bortezomib as part of induction and maintenance improves PFS in all patients and OS in patients with the del 17 cytogenetic abnormality and those who present in renal failure.
- In transplant eligible patients, single agent lenalidomide is effective demonstrated improved PFS and in 2 of 3 studies, improved OS.

Introduction

Multiple myeloma (MM) is a neoplasm typical of the elderly, with median age at diagnosis of 70 years, and approximately 65% of patients older than 65 years.[1] Many advances have been made thanks to the use of autologous hematopoietic stem cell transplantation (AHSCT) and the introduction of the immunomodulatory drugs and the proteasome inhibitors. Incorporation of novel agents into induction has resulted in improved overall survival (OS) over the past decade[2,3]. Indeed, in a large group of 2981 patients with newly diagnosed MM, overall survival significant improved from 29.9 to 44.8 months in patients diagnosed in the last decade ($P<0.001$).[3] The agents that have most impacted on progression-free survival (PFS) and OS are thalidomide[4,5], lenalidomide[6,7] and bortezomib.[8-11] The alkylating agent cyclophosphamide in combination with bortezomib and dexamethasone generated comparable deep responses to bortezomib, lenalidomide and dexamethasone in a Phase II study.[12] These combination induction regimens improve the overall response and the depth of response by increasing the percentage of patients achieving complete responses (CR). Many MM patients will have disease progression or relapse and die of MM within 10 years of the initiation of therapy. Thus, there is a pressing need for improved induction regimens and for strategies to control disease with the long term goal of cure. Of note, sequential approaches consisting of induction followed by consolidation and maintenance

with novel agents have been recently tested with the attempt of improving the clinical benefit of current treatments.[13] Consolidation improves responses after induction therapy (and transplantation when applicable) and maintenance further delays relapse/progression with the ultimate goal of improving OS. Consolidation consists of two to four cycles of combination therapies and maintenance of continuous therapy, usually with single agents, until disease progression.[14] Maintenance therapy is suggested for both transplant-ineligible patients (usually elderly patients over 65 years) and transplant-eligible ones (patients younger than 65 years of age). However, no specific guidelines are available, and the optimal duration of maintenance remains to be established.[15]

Optimal MM maintenance therapy should maintain or increase response after induction and, when possible, AHSCT. Maintenance therapy should be easily given (preferably oral) and if administered intravenously, convenient for the patient. Due to the lack of long term efficacy and tolerability, agents such as melphalan, interferon-α and glucocorticoids have not become widely used for maintenance[16-19]. Newer agents are more attractive as maintenance therapies due to improved efficacy and better tolerability. The majority of maintenance studies have used thalidomide and more recently, bortezomib and lenalidomide. Different studies have assessed the benefits associated with maintenance treatment incorporating thalidomide, lenalidomide and bortezomib, yet no clinical study has directly compared the advantages of one approach over the other. Despite the benefits associated with continuous novel-agent-based therapy, prolonged exposure to new drugs may increase toxicities and cause treatment discontinuation. Therefore the optimal maintenance therapy must be effective with minimal toxicity and should be easily administered.[20]

Maintenance approaches for patients ineligible for transplantation

Patients over 65 years of age do not tolerate intensive therapy and are usually ineligible for high-dose melphalan (MEL200; melphalan 200 mg/m^2) and AHSCT). For these patients gentler strategies should be used. Combinations with novel agents, such as thalidomide, lenalidomide and bortezomib, are widely adopted, both for newly diagnosed and relapse patients with MM. In the 1970s, maintenance treatment for this subset of patients consisted of prolonging chemotherapy after successful induction treatment with melphalan-prednisone (MP).[21-23] Other attempts of maintenance therapies consisted of using single-agent interferon.[24,25]

Thalidomide

Thalidomide can be a suitable option for prolonged use because of the oral administration. Nevertheless, the neurological toxicity associated with this drug is a major concern and should be carefully considered. To date, continuous thalidomide after melphalan-prednisone-thalidomide (MPT) induction has been evaluated in four of the trials (*Table 1*).[5,26-29] In one study, 100 mg/day thalidomide was given continuously. The median progression-free survival (PFS) was 25 months for patients who received thalidomide and 15 months for those who did not (P<0.001). The median OS was 48 months and 45 months for the two arms, respectively (P=0.79).[5,26] The incidence of grade 3-4 neurological toxicity was 10% in patients receiving thalidomide therapy and 1% in those receiving no maintenance. In another study, thalidomide was administered at 200 mg/ day at induction and was reduced to 50 mg/day during maintenance. The median event-free survival (EFS) time was 13 months for patients who received thalidomide and 9 months for those who did not (P<0.001). A marginally statistically significant OS advantage favoring thalidomide maintenance was also detected, with a median of 40 months versus 31 months (P=0.05).[27] The incidence of grade 3-4 neurologic toxicities was particularly higher with thalidomide (23%) than no thalidomide (4%). In another study, thalidomide at the dose of 200 mg/day was administered continuously until relapse.[28] The median PFS (15 months versus 14 months, P=0.84) and OS (29 months versus 32 months, P=0.16) was similar between patients who received thalidomide and those who did not. The incidence of grade 3-4 peripheral neuropathy was quite low in both arms, 6% versus 1%, respectively. These findings support the concept that thalidomide maintenance should be administered at the minimal effective dose associated with the lowest toxicity (50 to 100 mg/day) in order avoid early discontinuation.

Another randomized trial assessed the role of thalidomide-interferon or interferon alone as maintenance therapy after induction with either thalidomide-dexamethasone (TD) or MP.[30] The median PFS was 28 months for patients who received thalidomide maintenance and 13 months for those who received interferon alone (P=0.007). The median OS was similar in the two groups (53 months versus 51 months, P=0.81). The rate of grade 3-4 neuropathy was 7% versus 0%, respectively (P=0.002). Finally, in another study, a total of 820 patients, both eligible and ineligible for AHSCT, were randomized to thalidomide maintenance or no maintenance. Patients ineligible for AHSCT had received melphalan-prednisone or cyclophosphamide-thalidomide-dexamethasone induction.[31] In these patients, thalidomide maintenance improved PFS (23 versus 15 months, P<0.001), and the advantage was more evident in patients who had received thalidomide also at induction. The median OS was not significantly different between the two arms (P=0.40). In patients with adverse iFISH, thalidomide maintenance had a negative impact on OS (P=0.009).
All the studies including thalidomide maintenance reported an improvement in terms of PFS, although longer follow-up is needed to detect an OS benefit. The risk of peripheral neuropathy after long-term thalidomide exposure is a major limitation to its routine use. To avoid excessive neurologic toxicity and consequently treatment discontinuation, the preferred dose of thalidomide maintenance should range between 50 and 100 mg/day.[32] In case of occurrence of grade 3-4 neurotoxicity it is highly recommended to temporarily interrupt treatment until resolution to at least grade 1, otherwise treatment should be stopped.

Lenalidomide

Lenalidomide, similarly to thalidomide, is administered orally and has the additional advantage of lower neurologic toxicity.
A phase 3 study evaluated the role of lenalidomide at 10 mg on days 1-21 of each 28-day cycle after melphalan-prednisone-lenalidomide (MPR-R) versus MPR versus MP.[33] The median PFS was 31 months with MPR-R, 14 months with MPR and 13 months with MP. In a landmark analysis from start of lenalidomide maintenance, lenalidomide after MPR significantly prolonged the median PFS from 7 to 26 months (P<0.001). No particular advantage was seen in terms of OS, and the 4-year OS was approximately 58% in the three treatment groups. One of the major toxicity associated with lenalidomide is neutropenia, which was reported in 7% of patients in the MPR-R arm. Some concerns about the increased risk of second primary malignancies (SPM) with prolonged exposure to lenalidomide were raised. In this study, the rate of SPM was 7% for both MPR-R and MPR, and 3% for MP. Nevertheless, the benefits associated with lenalidomide treatment outweigh the increased risk of SPM. A recent meta-analysis on 3218 patients found that patients treated with lenalidomide had an increased risk of developing hematological SPM (HR 1.55; p=0.037). Of note, the risk was increased when lenalidomide was given with melphalan compared with melphalan alone (HR 4.86; p<0.0001), while exposure to lenalidomide plus cyclophosphamide (HR 1.26; p=0.75) or lenalidomide plus dexamethasone (HR 0.86; p=0.76) did not increase haematological SPM risk versus melphalan alone. Thus the use of alternative alkylating agents can be a possible option.[34]
A phase 2 study evaluated a sequential approach consisting of lenalidomide-prednisone (RP) induction followed by MPR consolidation and subsequent RP maintenance (lenalidomide 10 mg/day on days 1-21 of each 28-day cycle; prednisone 25 mg three times/week).[35] Median age was 75 years, 59% of patients had at least one comorbidity and 35% at least two. Median PFS was 18.4 months and 2-year OS was 80%. Grade 4 neutropenia occurred in 12% of patients. Therefore, this study demonstrated that the addition of prednisone increases the efficacy of lenalidomide alone in unfit elderly MM patients, with the advantage of a low toxicity and consequently improved quality of life.
A recent large phase 3 study compared lenalidomide plus low dose dexamethasone (Rd) until relapse versus Rd for 18 cycles (72 weeks) versus MPT for 12 cycles (72 weeks).[36] Median age was 73 years. After a median follow-up of 37 months, Rd significantly improved PFS compared with MPT (HR 0.72; p=0.00006) and marginally OS (HR 0.78, p=0.01685). Relevant grade 3-4 adverse events with Rd until relapse versus MPT were neutropenia (28% versus 45%), thrombocytopenia (8% versus 11%), febrile neutropenia (1% versus 3%), infection (29% versus 17%), neuropathy (5% versus 15%), and deep-vein thrombosis (5% versus 3%). The respective

incidence of hematologic SPM was 0.4% versus 2.2%; the overall incidence of solid tumors was identical (2.8%). These results suggest the need for prolonging therapy until progression, since outcome after 18 cycles of therapy was similar between Rd and MPT. Continuous Rd is therefore a valid option in transplant-ineligible patients, and may be preferred to the standard MPT with no maintenance.

Although elderly patients are usually not able to tolerate MEL200 and AHSCT, reduced intensity transplantation with melphalan 100 mg/m^2 (MEL100) can be safely adopted for fit elderly patients. A phase 2 study assessed bortezomib-adriamicyn-dexamethasone (PAD) induction followed by tandem MEL100, AHSCT, lenalidomide-prednisone consolidation and lenalidomide maintenance in patients aged 65 to 75 years.[37] This approach induced a median PFS of 48 months and a 5-year OS of 63%. Consolidation and maintenance with lenalidomide considerably increased responses, mostly in subjects who had achieved a very good partial response after transplantation. During consolidation and maintenance, the main toxicities were hematological; in particular, neutropenia (19% after consolidation and 23% after maintenance) and thrombocytopenia (15% after consolidation and 3% after maintenance).

Based on the data available, lenalidomide seems to be the most suitable choice for maintenance and can be preferred to thalidomide because of the higher efficacy and the lack of neurologic toxicity.

Bortezomib

Bortezomib is another possible option as maintenance therapy. Peripheral neuropathy associated with this drug may be a limitation, yet its incidence is lower than that reported with thalidomide.

In one study, bortezomib plus either thalidomide (VT) or prednisone (VP) was given after induction with either VMP or bortezomib-thalidomide-prednisone (VTP).[38] The median PFS was longer with VT (32 months) than VP (24 months), yet this difference was not statistically significant (P=0.1). No OS advantage favoring one of the two options was detected, and the incidence of peripheral neuropathy was slightly higher with VT (7%) than VP (2%).

In another study, bortezomib-melphalan-prednisone-thalidomide (VMPT) induction followed by VT maintenance (VMPT-VT) was compared with VMP followed by no maintenance.[39] VT consisted of bortezomib at 1.3 mg/m^2 every 15 days and thalidomide at 50 mg per day for 2 years or until progression or relapse. The median PFS was significantly longer with VMPT-VT (35.3 months) than with VMP (24.8 months; HR 0.58; P<0.001). The 5-year OS was greater with VMPT-VT (61%) than with VMP (51%; HR 0.70; P=0.01). Of note, the use of once-weekly bortezomib instead of twice-weekly administration appeared to be an appropriate strategy to improve tolerability and decrease discontinuation.[40] During the maintenance phase with VT, the incidence of new or worsened grade 3-4 toxicities was low (less than 5%). Grade 3-4 neutropenia was reported in four patients (3%), peripheral neuropathy in six patients (4%), and cardiologic adverse events in two patients (1%).

Another study assessed the role of bortezomib alone as maintenance therapy (1.6 mg/m^2, d 1, 8, 15, 22 for five 35-day cycles) after induction with bortezomib-dexamethasone (VD), bortezomib-thalidomide-dexamethasone (VTD), or VMP.[41] The median PFS was 14.7 months with VD, 15.4 months with VTD, and 17.3 months with VMP. The respective median OS was 49.8, 51.5, and 53.1 months. Grade 3-4 adverse events were lower with VD (78%) than VTD (87%) and VMP (83%). Bortezomib maintenance was associated with limited additional toxicity compared with induction.

A recent study evaluated the role of a sequential strategy with VMP followed by Rd versus the same regimens in an alternating approach. A total of 18 cycles was planned for both approaches.[42] After a median follow-up of 12 months, the 18-month time-to-progression was 83% with the sequential strategy and 89% with the alternating approach. A trend in favour of the alternating approach was seen in patients with high-risk cytogenetics profile (84% versus 94%). The respective 18-month OS was 83% and 93%. Yet, the difference between the two options was not statistically significant. Hematologic toxicities were lower in the sequential strategy (neutropenia: 16% versus 23%; thrombocytopenia: 16% versus 20%). Non-hematologic toxicities were low, with infections being the most common (5% versus 4% respectively). Both the sequential and the alternating approaches proved to be feasible and well tolerated.

In conclusion, bortezomib induces a lower rate of peripheral neuropathy than thalidomide, and maintenance with bortezomib plus thalidomide is effective and safe in patients ineligible for MEL200 and AHSCT. The lack of SPM and the possibility of the subcutaneous administration make bortezomib an advantageous strategy for maintenance. Although combining two agents associated with a potential risk of neurotoxicity can be a concern, the use of reduced dose intensities makes VT a valid maintenance option. Alternating VMP and Rd is an appealing option, particularly in high-risk patients, but further investigation is needed.

Maintenance approaches for patients eligible for transplantation

The paradigm in 2014 for transplant-eligible patients consists of induction, stem cell mobilization, AHSCT followed by consolidation and/or maintenance[43,44]. Recent studies have demonstrated improved outcomes in transplant-eligible patients receiving maintenance therapy and new approaches to consolidation and maintenance are currently being investigated for transplant eligible patients. This portion of the review focuses on maintenance therapy following AHSCT for transplant-eligible MM patients.

Thalidomide

The maintenance thalidomide studies resulted in improved EFS or PFS with OS that were improved, no different from maintenance or worse for selected high risk patients (Table 2). Four Phase III studies studied thalidomide maintenance until progression[32,45-48]. (Table 2) The Intergroupe Francophone du Myelome (IFM) randomized 400 patients after AHSCT to thalidomide versus no maintenance and demonstrated an improved 3-year EFS (52% versus 37%, P<0.009) and an improved 4 year OS (87% versus 75%, P<0.04)[32]. A United States of America (USA) single institution study from the Arkansas group demonstrated a significant benefit for thalidomide versus no thalidomide maintenance. The 5-year EFS was 64% for thalidomide and 43 % for no maintenance (P<0.001) and the 8 year OS was 57% for thalidomide versus 44% for no maintenance (P=0.09)[45]. A Stichting Hemato-Oncologie voor Volwassensen Nederland (Dutch-Belgian Cooperative Trial Group for Hematology Oncology) (HOVON) compared thalidomide and interferon-α maintenance and demonstrated that thalidomide improved the median EFS (34 versus 22 months, P<0.001) and resulted in a non-significant increase in median OS (73 versus 60 months, P=0.77)[46]. The Medical Research Council of the United Kingdom (MRC UK) Myeloma IX study examined intensive (transplant) and non-intensive (non-transplant) approaches for the treatment of newly diagnosed MM patients. For the transplant arm, thalidomide maintenance resulted in a median PFS of 22 months versus 15 months for the no maintenance arm (P<0.0001). The median OS was 60 months in both groups (P=0.70)[47,48]. The median PFS benefit due to thalidomide maintenance was seen only in the patients with low risk cytogenetics analyses at diagnosis (29 versus 18 months, P=0.01) but without OS benefit. For patients with high risk cytogenetic analyses, the OS was inferior for patients receiving thalidomide maintenance when compared to no maintenance (35 versus 47 months, P=0.01).

There have been four studies that have examined thalidomide plus glucocorticoids as maintenance after AHSCT[49-52]. An Australian study compared 243 patients receiving one year of thalidomide with prednisolone until progression to patients receiving prednisolone alone until progression[49]. The 3-year PFS for the thalidomide/prednisolone arm 42% and 23% for prednisolone only arm (P<0.001). The 3-year OS for the thalidomide/prednisolone arm was 86% and 75% for the prednisolone only arm (P=0.004). A USA trial, BMT-CTN 0102 compared AHSCT followed by reduced-intensity allogeneic HSCT with tandem AHSCT as the primary objective[50]. Patients were assessed as low or high risk based on clinical and cytogenetic features. The tandem AHSCT patients received Thalidomide and dexamethasone maintenance or observation alone. Following the first AHSCT, the 3-year PFS for low (standard) risk MM patients randomized to thalidomide and dexamethasone was 49% and 43% in the observation arm (P=0.08). There was no difference in the 3-year OS: 80% for the thalidomide and dexamethasone arm and 81% for the observation group (P=0.82). A Brazilian study studied 108 MM patients receiving single AHSCT by randomizing them to 12 months of either thalidomide and dexamethasone or dexamethasone alone maintenance[51]. The 2-year PFS was 64% for the thalidomide and dexamethasone arm and 30% for the dexamethasone only arm (P=0.002). There was no difference in the 2 year OS: 85% for the thalidomide and dexamethasone arm and 70% for the dexamethasone alone arm (P=0.27).

The National Cancer Institute of Canada Clinical Trials Group (NCIC CTG) and the Eastern Cooperative Oncology Group (ECOG) maintenance study randomized 332 MM patients receiving a single AHSCT to thalidomide and prednisone versus observation after AHSCT[52]. The PFS for thalidomide-prednisone was superior to observation: (4-year estimates: 32% vs. 14%; HR=0.56; P<0.0001). At 4 years median follow-up, the OS was 68% for thalidomide and prednisone and 60% for observation (P=0.18). Lower or standard risk MM patients benefited the most from maintenance therapy. Prolonged maintenance was not tolerated by a significant proportion of patients in all of the thalidomide studies.

Zoledronate

Zoledronate was compared to clodronate as supportive care during induction and maintenance therapy for MM patient receiving intensive (including AHSCT) and non-intensive (non-AHSCT) therapy for the initial treatment[48,53]. The primary maintenance question was the use of thalidomide therapy until progression with a secondary objective asking if every 3 to 4 week zoledronate therapy until progression would result in less skeletal related events than daily oral clodronate. In the early report, for AHSCT patients, the median OS was not reached for the zoledronate arm and was 62 months for clodronate arm. (HR 0.84, 95% CI, 0.68–1.03; P=0.0854). When combining both intensive and non-intensively treated patients, the median PFS was significantly longer in patients randomized to zoledronate when compared to patients randomized to clodronate (19 versus 18 months; HR 0.89; 95% CI, 0.80–0.98; P=0.02). The median OS was significantly longer for patients receiving zoledronate (52 versus 46 months; HR, 0.86; 95% CI, 0.77–0.97; P=0.01. There were more incidence of osteonecrosis of the jaw (ONJ) with zoledronate versus clodronate (3.7% versus 0.5%; P<0.0001) and most ONJ events were considered low-grade. These results imply that zoledronate may have an anti-MM effect as has been previously described[54]. Recent recommendations for bisphosphonate therapy were monthly for a year than change to every 3 months in year two then stop[55]. The early recognition and management of ONJ, the superiority of long term use of zoledronate over pamidronate for decreasing skeletal-related events[56] and the MRC IX trial results give consideration for zoledronate therapy until progression or at a minimum the continuation of zoledronate with active disease and resumption at disease progression[48].

Lenalidomide

There are two Phase III studies that have examined lenalidomide maintenance therapy after AHSCT[57,58]. A third study has reported preliminary results examining lenalidomide maintenance after chemotherapy or AHSCT[59]. A fourth study has examined lenalidomide alone versus lenalidomide plus prednisone after chemotherapy or AHSCT[60]. The studies are compared in Table 3.

The CALGB 100104 study randomized 462 newly diagnosed MM patients who had received various induction regimens to lenalidomide 10 mg daily (dose range 5 to 15 mg) versus placebo until progression after single AHSCT[57]. Of the induction regimens, 74% contained either thalidomide-or lenalidomide in combination with other agents. There was no pre- or post-AHSCT consolidation. The median time to progression (TTP) was 46 months for the lenalidomide arm and 27 months for the placebo arm (P<0.001). The 3 year PFS was 66% for the lenalidomide arm and 39% for the placebo arm (P<0.001). With a median follow-up of 34 months the 3-year OS rate for the lenalidomide arm was 88% and 80% for the placebo arm (P=0.028). The primary endpoint of TTP was met early and the study was un-blinded 22 months prior to this analysis when 86 of 128 eligible (non-progressing) placebo arm patients crossed over and began lenalidomide. Despite the cross-over, there has been a persistent TTP and OS benefit for the lenalidomide arm. An updated analysis was performed in 2013 at a median follow-up of 48 months, the OS was 80% for the lenalidomide group and 70% for the placebo group (P=0.008)[61]. A PFS advantage persisted for the lenalidomide arm. Patients receiving lenalidomide had an increased incidence of hematologic toxicities (neutropenia and thrombocytopenia) as well as an increase in SPM. There were 8/231(3.5%) hematologic malignancies, primarily myeloid malignancies (Acute Myeloid Leukemia/Myelodysplastic Syndrome (AML/MDS) n=6) on the lenalidomide arm and 1/229 (0.4%), Non-Hodgkin Lymphoma (NHL) n=1 on the placebo arm. There were 10/231 (4.3%) versus 5 (2.1%) solid tumors on the lenalidomide and 4/231 (1.7%) on the placebo arm. The SPM cumulative incidence risk was greater for the lenalidomide arm (P<0.008). The cumulative

incidence risks of progressive disease (P<0.001) or death (P<0.002) were greater for the placebo arm. When counting events as progressions, deaths and SPMs, the median EFS was 43 months for the lenalidomide arm and 27 months for the placebo arm (P<0.001).

The IFM 05-02 study examined 605 patients randomized to lenalidomide at the same dose range as CALGB 100104 versus placebo until progression after single (79%) or two AHSCT (21%). After the first or second AHSCT, all patients received a 2 cycle consolidation treatment of 25 mg of lenalidomide for three weeks out of four at approximately day 60 to 120 days post-AHSCT. Induction regimens consisted of vincristine, doxorubicin and dexamethasone (VAD) or VD. Twenty-five percent of patients received pre-AHSCT consolidation with dexamethasone, cyclophosphamide, etoposide and cisplatin (DCEP). The median PFS was 41 months for the lenalidomide arm patients and 23 months for the placebo arm patients (P<0.001). At 4 years, the PFS was 43% for the lenalidomide arm patients and 22% for the placebo arm patients (P<0.001). At a 45 month median follow-up, the OS was 74% for the lenalidomide arm and 76% for the placebo arm. The 4-year OS rates were 73% for the lenalidomide arm and 75% for the placebo arm (P=0.7). The study was also un-blinded 22 months prior to analysis. All maintenance was stopped at a median time of 2 years (range 1-3 years). There was no cross over for the placebo arm patients. This study was updated recently[62]. Now, with a median follow up of 60 months from randomization, the lenalidomide arm had an improved PFS (42%) compared to the placebo arm (18%) (P<0.0001). At 5 years, the OS for the lenalidomide arm is 68% and 67% for the placebo arm (HR=1). After first progression, the median survival is 29 months for the lenalidomide arm and 48 months for the placebo arm (P<0.0001). There was an increased incidence of hematologic toxicities (primarily neutropenia and thrombocytopenia) and increased incidence of SPMs in the lenalidomide arm. There were 13/306(4.2%) hematologic malignancies primarily lymphoid malignancies (acute lymphocytic leukemia (ALL) and Hodgkin lymphoma (HL) n=7, for lenalidomide arm patients and 5/302 (1.6%) primarily AML/MDS n=4, for the placebo arm patients. For solid tumors, there were 10/306 (3.3%) in lenalidomide arm patients and 4/302 (1.3%) in placebo arm patients. The median EFS (including progressions, deaths and SPMs) was 40 months for the lenalidomide arm and 23 months for the placebo arm (P<0.001).

The third lenalidomide maintenance study following chemotherapy (melphalan, prednisone, lenalidomide) versus tandem AHSCT with high-dose melphalan (MPR versus MEL200) has been reported[59]. Both chemotherapy and tandem AHSCT maintenance patients were combined and compared to those chemotherapy and tandem AHSCT patients who did not receive lenalidomide maintenance. At 49 months median follow-up, from chemotherapy or tandem AHSCT and at 35 months median follow-up from randomization to lenalidomide maintenance or no maintenance, the 3-year PFS for the lenalidomide maintenance patients was 37 months and 26 months for patients not receiving maintenance (P<0.0001). Five-year OS estimates were 75% for the lenalidomide arm and 58% for the no maintenance arm (P=0.02). The rate of SPMs was 4.5% in both maintenance arms (chemotherapy and tandem AHSCT). Another GIMEMA study examined maintenance therapy with lenalidomide plus prednisone versus lenalidomide alone following chemotherapy (cyclophosphamide, lenalidomide, prednisone) versus tandem AHSCT (CRD versus MEL200) in 389 newly diagnosed MM patients[60]. The chemotherapy and tandem AHSCT patients randomized to receive lenalidomide/prednisone maintenance were combined and compared to the chemotherapy and tandem AHSCT patients who were randomized to receive lenalidomide alone. At 31 months median follow-up from chemotherapy or tandem AHSCT, the 3-year PFS for lenalidomide/prednisone arm was 60% and 38% for lenalidomide alone (P=0.003). There was no difference in 3-year OS.

A meta-analysis of IFM 05 02, CALGB 100104, MPR vs Mel200 and MM 015[33] (a non-transplant trial) found that lenalidomide maintenance when compared to placebo improves PFS with a trend to an OS benefit[63]. Table 4 compares the differences between CALGB 100104 and IFM 05-02 which may help to explain the differences in OS, and types of SPM. In particular, there are differences in induction regimens, number of transplants, use of consolidation pre and post AHSCT and length of maintenance therapy.

The SPM etiologic risk factors are not fully defined. MM and monoclonal gammopathy of unknown significance (MGUS) have been associated with the development of AML/MDS[64]. In this registry study, MGUS patients would have not received therapy implying that there is an undefined stem cell defect in MGUS patients and by inference MM patients (who have the addition risk of

chemotherapy exposure) predisposing to the development of myeloid malignancies. A recent meta-analysis of 7 randomized controlled trials of more than 3000 newly diagnosed MM patients found that those who received lenalidomide had an increased risk of developing hematological SPMs, driven mainly by treatment strategies that included a combination of lenalidomide and oral melphalan[34]. Lenalidomide treatment with intravenous melphalan and other agents did not carry as high a risk as oral melphalan for the development of SPMs. Furthermore, with lenalidomide therapy, the risk of dying from MM or treatment-related adverse events remained higher than the risk of death due to SPMs. The HOVON-65/GMMG-HD4 two-year bortezomib maintenance was not associated with an increase in SPM[65]. The risk of SPM needs to be factored and balanced against the beneficial effects on PFS and OS when patients and clinicians decide on the use of maintenance treatment. So far there is no OS benefit with is seen with the recent IFM 05-02 analysis. Future and ongoing studies should facilitate the understanding of the optimal maintenance strategies for long term control of MM.

The IFM 05-02, MRC UK Medical Research Council United Kingdom IX, PETHEMA, HOVON 65 GMMG HD4 studies used induction regimens that are being superseded by novel agent combinations. The CALGB 100104 study contained patients who received older thalidomide-based induction regimens in addition to lenalidomide-containing regimens. Thus, we need to evaluate these studies relative to the induction regimens in use today. New studies incorporating newer agents, in particular bortezomib and lenalidomide are underway and are described later in this review. Unlike induction regimens, the standard AHSCT conditioning regimens remains high dose melphalan alone or in combination with agents such as bortezomib.

MM patients receiving induction therapy followed by consolidation with high dose melphalan and AHSCT often will have disease progression and relapse. Therefore, maintaining disease response is an important goal for MM management after AHSCT. Depth of response as manifested by the presence or absence of minimal residual disease correlates with long term disease control[66,67]. However factors such as disease staging, cytogenetics, and gene expression profiling predict long term outcome[68]. Thus, there have been attempts to incorporate cytogenetic risk factors and minimal residual disease detection[69]. Determining the most effective combination of induction, transplant dose intensive therapy, consolidation and maintenance will be accomplished with a goal of improved survival endpoints, patient tolerance and patient quality-of-life.

AHSCT is a standard approach to the management of transplant-eligible MM patients after induction therapy. The superiority of AHSCT over prolonged lower dose therapy has been demonstrated before use of bortezomib and lenalidomide in induction therapy[70,71]. A recent phase III study has shown a superior PFS and OS for early tandem transplant versus continued lower dose therapy. There are recently completed and ongoing phase III studies that examine the utility of upfront versus delayed AHSCT, the role of consolidation and single versus tandem AHSCT and the use of maintenance therapy[72-75]. The recently completed STAMINA trial (Stem cell transplant with lenalidomide maintenance in patients with multiple myeloma), BMT-CTN 0702 compared single, tandem AHSCT and single AHSCT followed by lenalidomide, bortezomib and dexamethasone consolidation[72]. Induction regimens were at the discretion of the enrolling centers. Originally all three arms were to be followed by lenalidomide maintenance for 3 years. The protocol has been amended to extend maintenance until progression. The European Myeloma Network (EMN) trial, Study to Compare VMP With HDM Followed by VRD Consolidation and Lenalidomide Maintenance in Patients With Newly Diagnosed Multiple Myeloma EMN 2 (HO95) will treat all NDMM patients with an induction regimen of bortezomib, cyclophosphamide and dexamethasone. Patients are randomized to three arms: bortezomib, melphalan, prednisone therapy, single or tandem AHSCT. After completion of this segment of the protocol, patients will either receive no consolidation versus consolidation with lenalidomide, bortezomib and dexamethasone before all patients receive lenalidomide maintenance until progression[73]. The Dana Farber Cancer Institute (DFCI 10-106) (IFM DFCI 2009) randomized trial compares 8 cycles of lenalidomide, bortezomib and dexamethasone, cyclophosphamide mobilization of hematopoietic stem cells and AHSCT at relapse with 3 cycles of lenalidomide, bortezomib and dexamethasone, cyclophosphamide mobilization of hematopoietic stem cells and upfront AHSCT followed by 2 cycles of lenalidomide, bortezomib and dexamethasone consolidation[74]. The IFM will treat patients with one year of lenalidomide maintenance. The study in the USA has been changed to maintenance lenalidomide until progression. The MRC myeloma XI trial, a randomised comparison

of thalidomide and lenalidomide combinations in myeloma patients of all ages will enroll patients on either an intensive (transplant) pathway or a non-intensive (non-transplant) pathway[75]. The intensive pathway compares two induction regimens and examines consolidation or no consolidation pre-AHSCT for patients with less than a VGPR. After single AHSCT, patients will be randomized to no maintenance or lenalidomide maintenance until disease progression.

Bortezomib

Bortezomib, the first proteasome inhibitor approved for the treatment of MM has been studied as both part of induction and maintenance therapy. The HOVON-65/German-speaking-Myeloma Multicenter Group (GMMG)-HD4 randomized 827 symptomatic and newly diagnosed MM patients to either of two induction regimens: VAD or PAD[65]. After induction all patients underwent stem cell mobilization with cyclophosphamide, doxorubicin and dexamethasone with granulocyte colony-stimulating factor followed by stem cell collection. Some high risk patients received eligible for allogeneic HSCT: VAD: 5% and PAD: 7%. German patients underwent tandem AHSCT due to clinical practice. The majority of patients VAD: (84%) and PAD patients: (85%) underwent single or tandem AHSCT followed by 2 years of maintenance. The VAD arm received thalidomide and the PAD arm received bortezomib. The study was first reported at a median follow-up of 41months. The median PFS for the PAD-P arm 35 months and for the VAD-T arm was 28 months (P=0.002) (Table 5). The multivariate analysis established a HR for PAD-P of 0.77 (95% CI, 0.60 to 1.00, P=0.049. Patients with the poor risk cytogenetic feature of del 17p13 receiving PAD-P had an improved median PFS (22 versus 12 months, (P=0.01)) and improved OS (not reached at 54 months versus 24 months, (P=0.003)) when compared to VAD-T. Patient in renal failure at diagnosis also had an improved PFS and OS when PAD-P when compared to VAD-T. There was no difference in PFS and OS for other cytogenetic risk groups. The Spanish Myeloma group, (Grupo Espanol de Mieloma (GEM) PETHEMA (Programa para el Estudio de la Terapéutica en Hemopatías Malignas) conducted a 386 patient trial that randomized newly diagnosed MM patients to 3 different induction treatments : VTD versus TD versus alternating chemotherapy: vincristine, carmustine, melphalan, cyclophosphamide, prednisone (VBMCP)/vincristine, carmustine, doxorubicin, dexamethasone (VBAD)[76]. Following induction, all eligible patients received a single AHSCT. All three induction groups were randomized to maintenance therapy for 3 years with interferon-α versus T or VT. At a median follow-up of 2 years from maintenance initiation, the PFS for the VT maintenance treatment was significantly longer than T or interferon-α (78% versus 63% versus 49%, P=0.01). For the 3 arms, there was no difference in OS (Table 2).

Summary

The introduction of novel agent-based maintenance therapy has considerably prolonged remission duration for MM patients. In transplant-ineligible patients, standard induction therapies consist of novel-agent based three-drug regimens. Two-drug regimens and gentler approaches with reduced doses are suggested in frail patients. The route of administration is fundamental while choosing maintenance therapy: thalidomide and lenalidomide have the advantage of the oral administration in comparison with intravenous bortezomib. Of note, in patients ineligible for transplantation, an OS benefit was reported with bortezomib maintenance while it was inconsistently detected with strategies including thalidomide and lenalidomide. The optimal maintenance approach should also be associated with a low toxicity to preserve quality of life. Peripheral neuropathy is a major concern with continuous thalidomide, less frequent with bortezomib, while it is less frequent with lenalidomide. Nevertheless, lenalidomide is associated with an increased risk of SPM. Future trials are needed to establish which option is the most suitable as maintenance therapy for transplant-ineligible subjects, and head-to-head comparisons are therefore necessary. The optimal duration of treatment is another crucial point that needs further investigation. In conclusion, the data available show that a sequential approach including induction therapy followed by consolidation and maintenance therapy is an appropriate and effective strategy in MM.

The current treatment standard for the transplant-eligible patient is induction therapy, preferably with 3 agents, including novel agents (proteasome inhibitor and or IMiD). Induction treatment is given to best response with the goal of attainment of CR. Trials in the USA and Europe will help define the optimal induction regimen, the role of single or tandem AHSCT or delayed AHSCT after

salvage therapy at relapse. Consolidation therapy following AHSCT is discussed in another chapter. Following AHSCT with or without consolidation, maintenance therapy is becoming a standard approach to maintain response and control disease long term. The optimal maintenance strategy will be defined with future studies.

Understanding risk should allow for developing strategies for long term disease control based on diagnostic disease characteristics. In addition to cytogenetic risk stratification, gene expression profiling (GEP) has been developed for defining high risk patients[77,78]. However, the optimal treatment approach for these high risk patients has yet to be defined and these high risk patients should be evaluated for new approaches. Novel drugs with novel mechanisms of action may offer strategies that could convert high risk disease into lower disease[79]. Ongoing studies will answer questions regarding the incorporation of new agents into induction treatment, the role of early versus delayed AHSCT, the role of consolidation and standard approaches to maintenance therapy to prolong and control disease and improve outcome.

Authorship: Philip McCarthy and Antonio Palumbo collected the data and wrote the manuscript.

Conflicts of interest: Dr. McCarthy has served on advisory boards and consulted for Celgene, Janssen, Millenium and Onyx. Dr Palumbo has received honoraria and consultancy fees from Celgene, Janssen-Cilag, Bristol-Myers Squibb, Millennium, Merck, and Onyx.

Acknowledgments: the authors wish to thank the editorial assistant Giorgio Schirripa

References:

1. Altekruse SF, Kosary CL, Krapcho M, et al. (eds). SEER Cancer Statistics Review, 1975-2007, National Cancer Institute. Bethesda, MD, http://seer.cancer.gov/csr/1975_2007/, based on November 2009 SEER data submission, posted to the SEER website 2010. Accessed January 2014.
2. Munshi NC, Anderson KC. New strategies in the treatment of multiple myeloma. *Clinical cancer research : an official journal of the American Association for Cancer Research* 2013; 19(13): 3337-44.
3. Kumar SK, Dispenzieri A, Lacy MQ, Gertz MA, Buadi FK, Pandey S et al. Continued improvement in survival in multiple myeloma: changes in early mortality and outcomes in older patients. Leukemia 2013.
4. Singhal S, Mehta J, Desikan R, et al. Antitumor activity of thalidomide in refractory multiple myeloma. N Engl J Med. 1999;341:1565-1571.
5. Palumbo A, Bringhen S, Musto P, et al. Oral melphalan, and prednisone chemotherapy plus thalidomide compared with melphalan and prednisone alone in elderly patients with multiple myeloma: randomized controlled trial. Lancet. 2006;367:825-831.
6. Richardson, P.G., Schlossman RL, Weller E, et al. Immunomodulatory drug CC-5013 overcomes drug resistance and is well tolerated in patients with relapsed multiple myeloma. Blood. 2002;100:3063-3067.
7. Rajkumar SV, Hayman SR, Lacy MQ, et al. Combination therapy with lenalidomide plus dexamethasone (Rev/Dex) for newly diagnosed myeloma. Blood. 2005;106:4050-4053.
8. Richardson PG, Barlogie B, Berenson J, et al. A phase 2 study of bortezomib in relapsed, refractory myeloma. N Engl J Med. 2003;348:2609-2617.
9. Harousseau JL, Attal M, Leleu X, et al. 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;91:1498-1505.
10. San Miguel JF, Schlag R, Khuageva NK, et al. Bortezomib plus melphalan and prednisone for initial treatment of multiple myeloma. N Engl J Med. 2008;359:906-917.
11. Cavo M, Tacchetti P, Patriarca F, et al. Bortezomib with thalidomide plus dexamethasone compared with thalidomide plus dexamethasone as induction therapy before, and consolidation therapy after, double autologous stem-cell transplantation in newly diagnosed multiple myeloma: A randomized phase 3 study. Lancet. 2010;376:2075-2085.
12. Kumar S, Flinn I, Richardson PG, et al.Randomized, multicenter, phase 2 study (EVOLUTION) of combinations of bortezomib, dexamethasone, cyclophosphamide, and lenalidomide in previously untreated multiple myeloma. Blood. 2012 10;119:4375-82.
13. Kumar SK, Rajkumar SV, Dispenzieri A, et al. Improved survival in multiple myeloma and the impact of novel therapies. Blood. 2008;111(5):2516–20.

14. Palumbo A, Rajkumar SV, San Miguel JF, et al. International Myeloma Working Group Consensus Statement for the Management, Treatment, and Supportive Care of Patients With MyelomaNot Eligible for Standard Autologous Stem-Cell Transplantation. J Clin Oncol. 2014;32(6):587-600.
15. Palumbo A, Anderson K. Multiple myeloma. N Engl J Med. 2011 Mar 17;364(11):1046-60.
16. Remission maintenance therapy for multiple myeloma. *Archives of internal medicine* 1975; 135(1): 147-52.
17. Belch A, Shelley W, Bergsagel D, Wilson K, Klimo P, White D *et al.* A randomized trial of maintenance versus no maintenance melphalan and prednisone in responding multiple myeloma patients. *British journal of cancer* 1988; 57(1): 94-9.
18. Fritz E, Ludwig H. Interferon-alpha treatment in multiple myeloma: meta-analysis of 30 randomised trials among 3948 patients. *Annals of oncology : official journal of the European Society for Medical Oncology / ESMO* 2000; 11(11): 1427-36.
19. Berenson JR, Crowley JJ, Grogan TM, Zangmeister J, Briggs AD, Mills GM *et al.* Maintenance therapy with alternate-day prednisone improves survival in multiple myeloma patients. *Blood* 2002; 99(9): 3163-8.
20. Ludwig H, Durie BG, McCarthy P, et al. IMWG consensus on maintenance therapy in multiple myeloma. Blood. 2012;119(13):3003-15.
21. Alexanian R, Balcerzak S, Haut A, et al. Remission maintenance therapy for multiple myeloma. Arch Intern Med. 1975;135(1):147-52.
22. Alexanian R, Gehan E, Haut A, et al. Unmaintained remissions in multiple myeloma. Blood. 1978;51(6):1005-11.
23. Belch A, Shelley W, Bergsagel D, et al. A randomized trial of maintenance versus no maintenance melphalan and prednisone in responding multiple myeloma patients. Br J Cancer. 1988;57(1):94-9.
24. Myeloma Trialists' Collaborative Group. Interferon as therapy for multiple myeloma: an individual patient data overview of 24 randomized trials and 4012 patients. Br J Haematol. 2001;113(4):1020-34.
25. Berenson JR, Crowley JJ, Grogan TM, et al. Maintenance therapy with alternate-day prednisone improves survival in multiple myeloma patients. Blood. 2002;99(9):3163-8.
26. Palumbo A, Bringhen S, Liberati AM, et al. Oral melphalan, prednisone, and thalidomide in elderly patients with multiple myeloma: updated results of a randomized controlled trial. Blood. 2008;112(8):3107-14.
27. Wijermans P, Schaafsma M, Termorshuizen F, et al. Phase III study of the value of thalidomide added to melphalan plus prednisone in elderly patients with newly diagnosed multiple myeloma: the HOVON 49 Study. J Clin Oncol. 2010;28(19):3160-6.

28. Waage A, Gimsing P, Fayers P, et al. Melphalan and prednisone plus thalidomide or placebo in elderly patients with multiple myeloma. Blood. 2010;116(9):1405-12.
29. Beksac M, Haznedar R, Firatli-Tuglular T, et al. Addition of thalidomide to oral melphalan/prednisone in patients with multiple myeloma not eligible for transplantation: results of a randomized trial from the Turkish Myeloma Study Group. Eur J Haematol. 2011;86(1):16-22. 7.
30. Ludwig H, Adam Z, Tóthová E, et al. Thalidomide maintenance treatment increases progression-free but not overall survival in elderly patients with myeloma. Haematologica. 2010;95(9):1548-54.
31. Morgan GJ, Gregory WM, Davies FE, et al. The role of maintenance thalidomide therapy in multiple myeloma: MRC Myeloma IX results and meta-analysis. Blood. 2012;119(1):7-15.
32. Attal M, Harousseau JL, Leyvraz S, et al. Maintenance therapy with thalidomide improves survival in patients with multiple myeloma. Blood. 2006;108(10):3289-94.
33. Palumbo A, Hajek R, Delforge M, et al. Continuous Lenalidomide Treatment for Newly Diagnosed Multiple Myeloma. N Engl J Med. 2012;366(19):1759-69.
34. Palumbo A, Bringhen S, Kumar SK, Lupparelli G, Usmani S, Waage A *et al.* Second primary malignancies with lenalidomide therapy for newly diagnosed myeloma: a meta-analysis of individual patient data. *Lancet Oncol.* 2014 Mar;15(3):333-42.
35. Falco P, Cavallo F, Larocca A, et al. Lenalidomide-prednisone induction followed by lenalidomide-melphalan-prednisone consolidation and lenalidomide-prednisone maintenance in newly diagnosed elderly unfit myeloma patients. Leukemia. 2013;27(3):695-701.
36. Facon T, Dimopoulos MA, Dispenzieri A, et al. Initial Phase 3 Results Of The First (Frontline Investigation Of Lenalidomide + Dexamethasone Versus StandardThalidomide) Trial (MM-020/IFM 07 01) In Newly Diagnosed Multiple Myeloma (NDMM) Patients (Pts) Ineligible For Stem Cell Transplantation (SCT). Blood. 2013;122:21(supplement) [abstract 2].
37. Gay F, Magarotto V, Crippa C, et al. Bortezomib induction, reduced-intensity transplantation, and lenalidomide consolidation-maintenance for myeloma: updated results. Blood. 2013;122(8):1376-83.
38. Mateos MV, Oriol A, Martínez-López J, et al. Bortezomib, melphalan, and prednisone versus bortezomib, thalidomide, and prednisone as induction therapy followed by maintenance treatment with bortezomib and thalidomide versus bortezomib and prednisone in elderly patients with untreated multiple myeloma: a randomised trial. Lancet Oncol. 2010;11(10):934-41.
39. Palumbo A, Bringhen S, Larocca A, et al. Bortezomib-Melphalan-Prednisone-Thalidomide Followed by Maintenance With Bortezomib-Thalidomide Compared With Bortezomib-

Melphalan-Prednisone for Initial Treatment of Multiple Myeloma: Updated Follow-Up and Improved Survival. J Clin Oncol. 2014 Jan 21. [Epub ahead of print]

40. Bringhen S, Larocca A, Rossi D, et al. Efficacy and safety of once-weekly bortezomib in multiple myeloma patients. Blood. 2010;116(23):4745-53.
41. Niesvizky R, Flinn I, Rifkin RM, et al. Efficacy and Safety Of Three Bortezomib-Based Induction and Maintenance Regimens In Previously Untreated, Transplant-Ineligible Multiple Myeloma (MM) Patients (Pts): Final Results From The Randomized, Phase 3b, US Community-Based UPFRONT Study (NCT00507416). Blood. 2013;122:21(supplement) [abstract 1966].
42. Mateos MV, Martínez-López J, Hernandez MT, et al. Comparison Of Sequential Vs Alternating Administration Of Bortezomib, Melphalan and Prednisone (VMP) and Lenalidomide Plus Dexamethasone (Rd) In Elderly Patients With Newly Diagnosed Multiple Myeloma (MM) Patients: GEM2010MAS65 Trial. Blood. 2013;122:21(supplement) [abstract 403].
43. Reece D. Update on the initial therapy of multiple myeloma. *American Society of Clinical Oncology educational book / ASCO. American Society of Clinical Oncology. Meeting* 2013: 307-12.
44. McCarthy PL, Hahn T.Strategies for induction, autologous hematopoietic stem cell transplantation, consolidation, and maintenance for transplantation-eligible multiple myeloma patients. *Hematology Am Soc Hematol Educ Program*. 2013:496-503.
45. Barlogie B, Pineda-Roman M, van Rhee F, Haessler J, Anaissie E, Hollmig K *et al.* Thalidomide arm of Total Therapy 2 improves complete remission duration and survival in myeloma patients with metaphase cytogenetic abnormalities. *Blood* 2008; 112(8): 3115-21.
46. Lokhorst HM, van der Holt B, Zweegman S, Vellenga E, Croockewit S, van Oers MH *et al.* A randomized phase 3 study on the effect of thalidomide combined with adriamycin, dexamethasone, and high-dose melphalan, followed by thalidomide maintenance in patients with multiple myeloma. *Blood* 2010; 115(6): 1113-20.
47. Morgan GJ, Gregory WM, Davies FE, Bell SE, Szubert AJ, Brown JM *et al.* The role of maintenance thalidomide therapy in multiple myeloma: MRC Myeloma IX results and meta-analysis. *Blood* 2012; 119(1): 7-15.
48. Morgan GJ, Davies FE, Gregory WM, Bell SE, Szubert AJ, Cook G *et al.* Long-term Follow-up of MRC Myeloma IX Trial: Survival Outcomes with Bisphosphonate and Thalidomide Treatment. *Clinical cancer research : an official journal of the American Association for Cancer Research* 2013; 19(21): 6030-8.
49. Spencer A, Prince HM, Roberts AW, Prosser IW, Bradstock KF, Coyle L *et al.* Consolidation therapy with low-dose thalidomide and prednisolone prolongs the survival of multiple myeloma patients undergoing a single autologous stem-cell transplantation

procedure. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2009; 27(11): 1788-93.

50. Krishnan A, Pasquini MC, Logan B, Stadtmauer EA, Vesole DH, Alyea E, 3rd *et al.* Autologous haemopoietic stem-cell transplantation followed by allogeneic or autologous haemopoietic stem-cell transplantation in patients with multiple myeloma (BMT CTN 0102): a phase 3 biological assignment trial. *The lancet oncology* 2011; 12(13): 1195-203.
51. Maiolino A, Hungria VT, Garnica M, Oliveira-Duarte G, Oliveira LC, Mercante DR *et al.* Thalidomide plus dexamethasone as a maintenance therapy after autologous hematopoietic stem cell transplantation improves progression-free survival in multiple myeloma. *American journal of hematology* 2012; 87(10): 948-52.
52. Stewart AK, Trudel S, Bahlis NJ, White D, Sabry W, Belch A *et al.* A randomized phase 3 trial of thalidomide and prednisone as maintenance therapy after ASCT in patients with MM with a quality-of-life assessment: the National Cancer Institute of Canada Clinicals Trials Group Myeloma 10 Trial. *Blood* 2013; 121(9): 1517-23.
53. Morgan GJ, Davies FE, Gregory WM, Cocks K, Bell SE, Szubert AJ *et al.* First-line treatment with zoledronic acid as compared with clodronic acid in multiple myeloma (MRC Myeloma IX): a randomised controlled trial. *Lancet* 2010; 376(9757): 1989-99.
54. Corso A, Ferretti E, Lazzarino M. Zoledronic acid exerts its antitumor effect in multiple myeloma interfering with the bone marrow microenvironment. *Hematology* 2005; 10(3): 215-24.
55. Terpos E, Morgan G, Dimopoulos MA, Drake MT, Lentzsch S, Raje N *et al.* International Myeloma Working Group recommendations for the treatment of multiple myeloma-related bone disease. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2013; 31(18): 2347-57.
56. Rosen LS, Gordon D, Kaminski M et al. Long-term efficacy and safety of zoledronic acid compared with pamidronate disodium in the treatment of skeletal complications in patients with advanced multiple myeloma or breast carcinoma: a randomized, double-blind, multicenter, comparative trial. Cancer 2003; 98: 1735–1744.
57. McCarthy PL, Owzar K, Hofmeister CC, Hurd DD, Hassoun H, Richardson PG *et al.* Lenalidomide after stem-cell transplantation for multiple myeloma. *The New England journal of medicine* 2012; 366(19): 1770-81.
58. Attal M, Lauwers-Cances V, Marit G, Caillot D, Moreau P, Facon T *et al.* Lenalidomide maintenance after stem-cell transplantation for multiple myeloma. *The New England journal of medicine* 2012; 366(19): 1782-91.
59. Gay F, Cavallo F, Caravita T, Cavalli M, Nagler A, Montefusco V *et al.* Maintenance Therapy With Lenalidomide Significantly Improved Survival Of Yong Newly Diagnosed Multiple Myeloma Patients *Blood* 2013 122:2089

60. Palumbo A, Gay F, Spencer A, Raimondo FD, Zdenek A, Larocca A *et al.* A phase III study of ASCT vs cyclophosphamide-lenalidomide-dexamethasone and lenalidomide-prednisone maintenance vs lenalidomide alone in newly diagnosed myeloma patients. *Blood* 2013; 122:763.
61. McCarthy P, Owzar K, Hofmeister CC, Richardson PG, Hassoun H, Stadtmauer EA *et al.* Analysis of Overall Survival (OS) in the Context of Cross-Over from Placebo to Lenalidomide and the Incidence of Second Primary Malignancies (SPM) in the Phase III Study of Lenalidomide Versus Placebo Maintenance Therapy Following Autologous Stem Cell Transplant (ASCT) for Multiple Myeloma (MM) CALGB (Alliance) ECOG BMTCTN. *Clinical Lymphoma Myeloma and Leukemia* 2013; 13(Supplement 1): S28,S15-5.
62. Attal M, Lauwers-Cances V, Marit G, Caillot D, Facon T, Hulin C *et al.* Lenalidomide Maintenance After Stem-Cell Transplantation For Multiple Myeloma: Follow-Up Analysis Of The IFM 2005-02 Trial. *Blood* 2013; 406a.
63. Singh PP, Kumar S, LaPlant BR, Gertz MA, Dispenzieri A, Leif Bergsagel P *et al.* Lenalidomide Maintenance Therapy In Multiple Myeloma: A Meta-Analysis Of Randomized Trials. *Blood* 2013; 407a.
64. Mailankody S, Pfeiffer RM, Kristinsson SY, et al. Risk of acute myeloid leukemia and myelodysplastic syndromes after multiple myeloma and its precursor disease (MGUS). *Blood* 2011;118:4086-92.
65. Sonneveld P, Schmidt-Wolf IG, van der Holt B, El Jarari L, Bertsch U, Salwender H *et al.* Bortezomib induction and maintenance treatment in patients with newly diagnosed multiple myeloma: results of the randomized phase III HOVON-65/ GMMG-HD4 trial. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2012; 30(24): 2946-55.
66. Paiva B, Vidriales MB, Cerveró J, et al. GEM (Grupo Español de MM)/PETHEMA (Programa para el Estudio de la Terapéutica en Hemopatías Malignas) Cooperative Study Groups. Multiparameter flow cytometric remission is the most relevant prognostic factor for multiple myeloma patients who undergo autologous stem cell transplantation. *Blood*. 2008;112:4017-4023.
67. Rawstron AC, Child JA, de Tute RM, Davies FE, Gregory WM, Bell SE et al. Minimal residual disease assessed by multiparameter flow cytometry in multiple myeloma: impact on outcome in the Medical Research Council Myeloma IX Study. *J Clin Oncol.* 2013 Jul 10;31(20):2540-7. doi: 10.1200/JCO.2012.46.2119. Epub 2013 Jun 3. Erratum in: *J Clin Oncol.* 2013 Dec 1;31(34):4383.
68. Chng WJ, Dispenzieri A, Chim CS, Fonseca R, Goldschmidt H, Lentzsch S et al. IMWG consensus on risk stratification in multiple myeloma. International Myeloma Working Group. *Leukemia*. 2014 Feb;28(2):269-77.

69. Paiva B, Gutierrez NC, Rosinol L, Vidriales MB, Montalban MA, Martinez-Lopez J *et al.* High-risk cytogenetics and persistent minimal residual disease by multiparameter flow cytometry predict unsustained complete response after autologous stem cell transplantation in multiple myeloma. *Blood* 2012; 119(3): 687-91.
70. Attal M, Harousseau JL, Stoppa AM, Sotto JJ, Fuzibet JG, Rossi JF *et al.* A prospective, randomized trial of autologous bone marrow transplantation and chemotherapy in multiple myeloma. Intergroupe Francais du Myelome. *The New England journal of medicine* 1996; 335(2): 91-7.
71. Child JA, Morgan GJ, Davies FE, et al. Medical Research Council Adult Leukaemia Working Party. High-dose chemotherapy with hematopoietic stem-cell rescue for multiple myeloma. N Engl J Med. 2003 May 8;348(19):1875-83.
72. Stem Cell Transplant With Lenalidomide Maintenance in Patients With Multiple Myeloma http://clinicaltrials.gov/ct2/show/NCT01109004
73. Study to Compare VMP With HDM Followed by VRD Consolidation and Lenalidomide Maintenance in Patients With Newly Diagnosed Multiple Myeloma EMN 2 (HO95) http://clinicaltrials.gov/ct2/show/NCT01208766
74. Randomized Trial of Lenalidomide, Bortezomib, Dexamethasone vs High-Dose Treatment With SCT in MM Patients up to Age 65 (DFCI 10-106) (IFM DFCI 2009) http://clinicaltrials.gov/ct2/show/NCT01208662
75. Thalidomide and lenalidomide combinations in newly diagnosed patients with symptomatic myeloma: a randomised, phase III, multi-centre, open-label trial. http://www.controlled-trials.com/ISRCTN49407852/myeloma+XI
76. Rosiñol L, Oriol A, Teruel AI, et al. Superiority of bortezomib, thalidomide, and dexamethasone (VTD) as induction pretransplantation therapy in multiple myeloma: a randomized phase 3 PETHEMA/GEM study. *Blood*. 2012;120:1589-96.
77. Shaughnessy JD Jr, Haessler J, van Rhee F et al. Testing standard and genetic parameters in 220 patients with multiple myeloma with complete data sets: superiority of molecular genetics. *Br J Haematol.* 2007; 137:530-6.
78. Kuiper R, Broyl A, de Knegt Y et al. A gene expression signature for high-risk multiple myeloma. Leukemia. 2012; 26:2406-13.
79. Ocio EM, Richardson PG, Rajkumar SV, Palumbo A, Mateos MV, Orlowski R *et al.* New drugs and novel mechanisms of action in multiple myeloma in 2013: a report from the international myeloma working group (IMWG). *Leukemia* 2014, 28:525-42.

Table 1. Main maintenance approaches for patients ineligible for MEL200 and transplantation

Drug	Study	Schedule	Response	Median PFS/TTP/EFS	Median OS	Previous induction
Thalidomide	Palumbo et al.[5,26]	T: 100 mg/day until relapse	16% CR	22 months	45 months	MPT
	Wijermans et al.[27]	T: 50 mg/day until relapse	23% ≥VGPR	13 months	40 months	MPT
	Waage et al.[28]	T: 200 mg/day until progression	13% CR	15 months	29 months	MPT
	Beksac et al.[29]	T: 100 mg/day until relapse	9% CR	21 months	26 months	MPT
	Ludwig et al.[30]	T: 200 mg/day until progression or intolerance; I: 3 Mega units three times a week	---	28 months	53 months	MP or TD
	Morgan et al.[31]	T: 50 mg/day increased to 100 mg/day after four cycles (if tolerated) until progression	---	23 months	---	MP or CTDa
Lenalidomide	Palumbo et al.[33]	R: 10 mg days 1-21 until disease progression	33% ≥VGPR	31 months	70% @ 36 months	MPR
	Gay et al.[37]	R: 25 mg days 1-21; P: 50 mg qod for four 28-day cycles *followed by* R: 25 mg days 1-21 until disease progression	48% CR 53% CR	48 months	63% @ 60 months	PAD-MEL100[§]
Bortezomib	Mateos et al.[38]	V: 1.3 mg/m^2 twice weekly, on days 1, 4, 8, 11, every 3 months; P: 50 mg qod for up to 3 years	39% CR	32 months	---	VMP or VTP
	Mateos et al.[38]	V: 1.3 mg/m^2 twice weekly, on days 1, 4, 8, 11, every 3 months; T: 50 mg/day for up to 3 years	44% CR	24 months	---	VMP or VTP
	Palumbo et al.[39]	V: 1.3 mg/m^2 every 14 days; T: 50 mg/day for 2 years	42% CR*	56% @ 36 months	61% @ 60 months	VMPT

T, thalidomide; I, interferon α-2b; R, lenalidomide; P, prednisone; V, bortezomib; MPT, melphalan-prednisone-thalidomide; MPR, melphalan-prednisone-lenalidomide; TD, thalidomide-dexamethasone; CTDa, cyclophosphamide-thalidomide-dexamethasone attenuated; PAD, bortezomib-doxorubicin-dexamethasone; MEL100, melphalan 100 mg/m^2; VMP, bortezomib-melphalan-prednisone; VTP, bortezomib-thalidomide-prednisone; VMPT, bortezomib-melphalan-prednisone-thalidomide; CR, complete response; VGPR, very good partial response; qod, every other day; PFS, progression-free survival; TTP time to progression; EFS, event-free survival; OS, overall survival; * by exploratory analysis performed on the 82 patients treated with VMPT induction who received at least 6 months of maintenance with VT; [§]Treatment approach incorporating transplantation before consolidation and maintenance, enrolling patients 65-75 years; MEL200, melphalan 200 mg/m^2

Table 2. Thalidomide with and without Glucocorticoid Maintenance following Autologous Hematopoietic Stem Cell Transplantation

Study	Number of patients	Initial Dose, milligrams	Maintenance versus no Maintenance	
			EFS or PFS	OS
Attal et al. [32]	597	400	3-year EFS **52 vs 37%** (P<0.009)	4-year OS **87 vs 75%** (P<0.04)
Barlogie et al. [45]	668	400	5-year EFS **64 vs 43%** (P<0.001)	8-year OS **57 vs 44%** (P=0.09)
Lokhorst et al. [46]	556	50	Median EFS **43 vs 22 months** (P<0.001)	Median OS **73 vs 60 months** (P=0.77)
Morgan et al. [47,48]	820	50	Median PFS (HSCT) **30 vs 23 months** (P=0.003)	3 year OS **75 vs 80%** (P=0.26)
Spencer et al. [49]	243	200 and prednisolone	3-year PFS **42 vs 23%** (P<0.001)	3-year OS **86 vs 75%** (P=0.004)
Krishnan et al. [50]	436*	200 and dexamethasone	3 year PFS **49 vs 43%** (P=0.08)	3 year OS **80 vs 81%** (P=0.817)
Maiolino et al. [51]	108	200 and dexamethasone	2 year PFS **64 vs 30%** (P=0.002)	2 year OS **85 vs 70%** (P=0.27)
Stewart et al. [52]	332	200 and prednisone	4 year PFS **32 vs 14%** (P<0.0001)	4 year OS **68 vs 60** (P=0.18)

This cohort was part of a larger 1910 patient study examining other non-transplant therapies. *This cohort was part of a larger 710 patient study examining allogeneic and autologous HSCT.
Abbreviations: EFS: Event-free survival; OS: Overall Survival; PFS: Progression-Free Survival Adapted with permission from McCarthy PL. Part I: the role of maintenance therapy in patients with multiple myeloma undergoing autologous hematopoietic stem cell transplantation. J Natl Compr Canc Netw. 2013 Jan 1;11(1):35-42.

Table 3. Lenalidomide alone or with glucocorticoid maintenance after Autologous Hematopoietic Stem Cell Transplantation

Study	Number of patients	Initial Dose, milligrams	Maintenance versus no Maintenance	
			EFS or PFS	OS
McCarthy et al [57]	460	10	TTP **46 vs 27months** (P<0.001)	Median followup 34 m **85 vs 77%** (P=0.028)
			3-year PFS rate **66%** (95% CI, 59 to 73) vs **39%** (95% CI, 33 to 48)	3 year OS rate **88 %** (95% CI, 84 to 93) vs **80 %** (95% CI, 74 to 86)
			EFS **43 vs 27 months** (P<0.001)	
McCarthy et al [61]				Median followup 48 m **80 vs 70%** (P=0.008)
Attal et al [58]	614	10	PFS **41 vs 23 months** (P<0.001)	Median followup 45 m **74 vs 76%** (P=0.7)
			4 year PFS **43 vs 22%** (P<0.001)	4 year OS **73 vs75%** (NS)
			EFS **40 vs 23 months** (P<0.001)	
Attal et al [62]			5 year PFS **42% vs 18%** (P<0.001)	Median followup 70 m 5 year OS **68 vs 67%** (NS)
Gay et al [59]	202 (NIT) 200 (IT)	10 (3 of 4 weeks monthly)	Landmark Analysis Median PFS (combining NIT and IT groups) **42 vs 18 months**(P <0.001)	4 year OS (combining NIT and IT groups) **80 versus 62%** (P=0.01)

Palumbo et al [60]	194 (NIT) 195 (IT)	10: days 1 to 21 of 28 days +/- **P** 50: every other day	3 year PFS (combining NIT and IT groups) RP: 60% vs 38% for R alone (P=0.003)	31 month median followup (combining NIT and IT groups) 3 year OS (NIT and IT) ND

EFS: Event-free survival includes deaths, progressions and second cancers; IT: Intensive Therapy; NIT: Non-intensive therapy; ND: No difference, NS: Not significant; OS: Overall Survival; P: Prednisone, PFS: Progression-Free Survival, R: Lenalidomide. Adapted with permission from McCarthy PL. Part I: the role of maintenance therapy in patients with multiple myeloma undergoing autologous hematopoietic stem cell transplantation. J Natl Compr Canc Netw. 2013 Jan 1;11(1):35-42.

Table 4. Differences between CALGB 100104 and IFM 05 02

Comparisons	CALGB 100104[57]	IFM 2005-02[58]
Induction	Thal- or Len-based (74%)	VAD (52%) and VD (44%)
Pre-AHSCT Consolidation	None	DCEP (25%)
Number of AHSCT	One	One (79%), Two (21%)
Post-AHSCT Consolidation before randomization	None	Len: 25 mg daily, 3 of 4 wks for 2 cycles pre-day ~100
Median F/Up at un-blinding	18 months	33 months
Median F/Up from randomization	46 months	64 months
Cytogenetic stratification	Not available	More high risk in len arm
Dosing schedule	10 mg (5 to 15 mg)	10 mg (5-15 mg)
Time from first patient enrolled	90 months	74 months
Placebo patients crossed over to lenalidomide at un-blinding	Yes (86 of 128 non-progressing patients)	No cross over
Second primary malignancies	3 fold increase	2.6 fold increase
Increase in AML/MDS	Yes	No
Increase in ALL/HL	No	Yes
Maintenance Stopped	No	Yes at a median of 2 years (range 1 to 3)
OS after progression*	No difference between arms	Worse for len than for placebo

AHSCT: autologous hematopoietic stem cell transplant; ALL/HL: acute lymphocytic leukemia/hodgkin lymphoma; AML/MDS: acute myeloid leukemia/myelodysplastic syndrome; DCEP: dexamethasone/cyclophosphamide/etoposide/cisplatin; Len: Lenalidomide; Thal: Thalidomide; VAD: vincristine/doxorubicin/dexamethasone; VD: bortezomib/dexamethasone; * Preliminary analysis Adapted with permission from McCarthy PL. Part I: the role of maintenance therapy in patients with multiple myeloma undergoing autologous hematopoietic stem cell transplantation. J Natl Compr Canc Netw. 2013 Jan 1;11(1):35-42.

Table 5. Bortezomib and Zoledronate Maintenance after Autologous Hematopoietic Stem Cell Transplantation

Study	Number of patients	Initial Dose	Maintenance versus no Maintenance	
			PFS	OS
Morgan et al [53]	1111 (IT) 8 (NIT)	Zoledronate: 4 mg IV every 3-4 wks or Clodronate 1600 mg orally daily	IT Median PFS **25 vs 25 months**	Median OS for IT patients **Not reached vs 62.5 months** HR, 0·84 (95% CI, 0·68–1·03) P=0·0854
				Median OS for all patients **50 vs 45.5 months** HR 0·87 (95% CI 0·77–0·99) p=0·04
Sonneveld et al [65]	827	Bortezomib: 1.3 mg/m^{2}IV every 2 weeks for 2 years or Thalidomide 50 mg daily	Median PFS **35 vs 28 months** (P=0.002)	Median follow-up 41 months OS (MV analysis) HR, 0.77 (95% CI , 0.60 to 1.00) P=0.049
			Landmark analysis for those without progression at 1 yr **45 vs 38% progression-free** P=0.05	5-year OS **61 vs 55%** P=0.07
Rosiñol et al. [76]	386	Bortezomib 1.3 mg/m^{2}IV on days 1, 4, 8, and 11 every 3 months with thalidomide100 mg per day orally or thalidomide 100 mg per day orally alone or Interferon alfa (3 million units SC 3 times weekly	2 year PFS at a median follow-up of 24 months **78 vs 63 vs 49%** P=0.01	OS not significantly different

SC: Subcutaneous; IT: Intensive Therapy; IV: Intravenous; NIT: Non-intensive therapy; MV: Multi-variate; OS: Overall Survival; PFS: Progression-Free Survival Adapted with permission from McCarthy PL. Part I: the role of maintenance therapy in patients with multiple myeloma undergoing autologous hematopoietic stem cell transplantation. J Natl Compr Canc Netw. 2013 Jan 1;11(1):35-42.