Efficacy and Safety of Busulfan-Based Conditioning Regimens for Multiple Myeloma

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ABSTRACT

Multiple myeloma is a malignancy of B cells characterized by accumulation of abnormal plasma cells in the bone marrow. In the past 20 years, the use of high-dose therapies and novel agents has resulted in significant and meaningful improvements in survival. Autologous stem cell transplantation (auto-SCT) following a high-dose melphalan-conditioning regimen represents the standard of care for younger patients as well as older patients with a good performance status. A number of strategies have been proposed to improve the outcome of auto-SCTs, including the incorporation of new agents such as thalidomide, lenalidomide, and bortezomib into the induction regimen administered before auto-SCT; the administration of maintenance therapy after auto-

SCT; the incorporation of novel agents into chemotherapeutic regimens after transplantation as consolidation therapy; and the use of reduced-intensity allogeneic transplantation after an initial autograft. Although these approaches have demonstrated some success in improving responses after auto-SCT, none of these strategies are curative. An additional strategy to improve outcomes after auto-SCT is to enhance the immediate pretransplant conditioning regimens by either increasing the dose of melphalan or by incorporating novel agents, such as busulfan. This literature review focuses on the efficacy and safety of busulfan-based conditioning regimens for auto-SCT in patients with multiple myeloma.

Implications for Practice: High-dose melphalan, as a single agent, has represented the standard conditioning regimen before autologous stem cell transplant in multiple myeloma for the last decade. Although formal phase 3 trials have not yet been performed, a systemic review of the literature indicates that the combination of high-dose melphalan and another alkylating agent, busulfan (the BU-MEL regimen), consistently produces longer progression-free survival than melphalan alone. The use of intravenous busulfan reduces the toxicity of this regimen. The combination of BU-MEL therefore represents one strategy to improve the results of stem cell transplantation and deserves further evaluation.

INTRODUCTION

Multiple myeloma (MM) is a malignancy of B cells characterized by an accumulation of abnormal plasma cells in the bone marrow [1]. Worldwide, MM represents approximately 1% of all reported cancers and 12%–15% of hematological malignancies [2]. In Canada, 2,400 patients are diagnosed with MM per year, with an incidence rate of 5 per 100,000 [3].

In the past two decades, the use of high-dose therapies and novel agents has resulted in a significant and meaningful improvement in median survival time, from 3 years in the 1960s to mid-1990s to approximately 5 years from the late 1990s to 2008 [4]. Despite advances in treatment, the disease remains largely incurable, with an annual death rate of 3 per 100,000 [5, 6]. Improving survival in MM there-

fore remains the primary goal of treatment [3]. Because response rates—particularly those reflecting a deeper level of myeloma cell kill, such as complete response (CR), near CR (nCR), and very good partial response (VGPR)—are strongly associated with improved overall survival (OS) and progression-free survival (PFS) times, they are often used to evaluate the efficacy of treatment as a surrogate for OS [7, 8]. However, to improve sensitivity, recent criteria such as stringent CR, which includes newer immunological tests, and minimal residual disease (MRD), which uses sensitive marrow assays to quantify tumor cells in the marrow, are being investigated as alternatives to traditional outcome measures [9].

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In younger patients (<65 years) and older fit patients (65–70 years with good performance status), the standard of care is autologous stem cell transplantation (auto-SCT), performed usually as part of initial therapy but occasionally at the time of disease relapse. Prior to auto-SCT, high-dose melphalan (MEL) (200 mg/m²) is the standard conditioning regimen, with a lower dose (140 mg/m²) given to patients older than 70 years or those with renal insufficiency to improve tolerability [10]. Although treatment with high-dose therapies followed by auto-SCT achieves improved CR and longer survival times compared with nontransplant approaches, this strategy is not curative and myeloma relapse remains the primary cause of death [11]. A single auto-SCT after older induction regimens typically produces a variably defined CR in 20%–40% of patients, with a median PFS time of 2.5–4 years and an OS time of 4–5 years [10].

A number of strategies have been proposed to improve the outcome of auto-SCTs. One strategy is to incorporate new agents such as thalidomide, lenalidomide, and bortezomib into the induction regimen administered before auto-SCT [10]. However, even with novel induction regimens, the median duration of response does not exceed 3 years following auto-SCT, with almost all patients experiencing progressive myeloma [12]. The use of tandem transplants (which increases the total amount of alkylating agent given) has also been shown to improve PFS time, with variable results shown for OS time. Studies suggest that tandem transplants show the most benefit in patients who fail to achieve a CR, nCR, or VGPR following initial auto-SCT [10].

Another strategy to improve outcomes is to administer maintenance therapy following auto-SCT. Older maintenance therapies such as IFN are not used routinely due to limited efficacy and poor tolerability [10]. Newer agents such as thalidomide, bortezomib, and lenalidomide may improve outcomes and are being examined in ongoing studies following auto-SCT. Of these agents, thalidomide has been studied most extensively, and its use consistently confers significant improvements in CR rates and PFS times, with an improvement in OS times found in some studies [13]. However, thalidomide is associated with considerable toxicity, which negatively impacts quality of life and limits the duration of administration [10]. More recent phase III studies indicate that the immunomodulatory derivative lenalidomide is much better tolerated in the maintenance setting; it also prolongs PFS and possibly OS times [6, 14]. Of note, the use of lenalidomide maintenance after auto-SCT has resulted in an unprecedented PFS time of 3.5 years in both of these phase III trials. Other strategies include different post-auto-SCT approaches, such as the incorporation of novel agents into chemotherapeutic regimens as “consolidation therapy” or use of reduced-intensity allogeneic transplantation after an initial autograft, which have also demonstrated some success in improving responses following auto-SCT.

A final strategy to improve outcomes after auto-SCT is to enhance the immediate pretransplant conditioning regimens by either increasing the dose of MEL or by incorporating novel agents. The incorporation of novel drugs into pretransplant conditioning regimens has not been well-studied, despite their widespread use as part of induction therapy [11] and the demonstration of promising results [15]. Increasing the dose of MEL beyond 200 mg/m² has improved CR rates to approxi-

mately 60%, but this improvement is limited by mucosal toxicity [10].

Alternatively, some groups have examined the addition of busulfan (BU) to more conventional conditioning regimens in an effort to improve outcomes following auto-SCT. BU is a bifunctional alkylating agent known chemically as 1,4-butanediol-dimethanesulfonate. In Canada, BU is indicated for use in MM in combination with other chemotherapeutic agents and/or radiotherapy as a conditioning regimen prior to hematopoietic progenitor cell transplantation [16]. This article presents the results of a literature review on the efficacy and safety of BU-based conditioning regimens for patients with MM who are eligible for auto-SCT.

METHODS

The reviewed literature was selected by conducting a systematic search of the PubMed database on February 14, 2011 with the keywords “busulfan” and “myeloma” in all fields, using the following limits “English or French”, “with abstracts”, and “on humans”. The search was also performed without limits to check for recent publications not yet fully indexed. Articles identified by the PubMed search were then screened by abstract. A final set of publications was selected based on the following inclusion criteria: (a) studies involving BU as a conditioning agent for transplant in patients with MM and (b) studies reporting safety or efficacy outcomes, such as adverse event (AE) rates, treatment-related mortality (TRM), nonrelapse mortality, response rates, PFS, or OS. Exclusion criteria included studies involving less than five patients treated with a BU-based regimen; publications involving other alkylating agents, such as treosulfan or hepsulfam; and studies on allogeneic hematopoietic stem cell transplantation.

Extraction of efficacy and safety data was performed for the publications that met these criteria. To present general trends in the extracted data, endpoints were aggregated across studies, when possible, by weighting each endpoint by the number of corresponding patients in the publication. All averages presented in this article are therefore sample size-weighted averages. A description of a sample-size weighted average methodology can be found in the study by Thakkar et al. [17].

RESULTS

A total of 129 abstracts were retrieved based on the PubMed database search with the keywords “busulfan” and “myeloma.” After a first screening by abstract, 90 publications were selected for full publication review. The final set of relevant publications was selected based on the inclusion/exclusion criteria described earlier. The selection procedure resulted in a total of 43 publications on auto-SCT (Fig. 1), of which two studies involved both autologous and allogeneic stem cell transplantations (Reynolds et al., 2001; Schiller et al., 1994).

Additionally, five publications reported results based on a subset or an interim analysis of a sample used in a subsequent study. These publications were therefore excluded from the analysis because their patient sample was duplicative of one used in another study. Across the final set of 38 publications, a total of 1,990 patients with MM received a BU-based conditioning regimen for auto-SCT, 1,376 patients (71%) received a BU-based conditioning regimen for upfront transplantation,

Figure 1. Study selection flowchart.

Abbreviations: auto-SCT, autologous stem cell transplantation; BU, busulfan; MM, multiple myeloma.

and 572 (29%) received a BU-based conditioning regimen for salvage auto-SCT. These figures do not add up to the total number of patients because they do not include study patients for whom the upfront versus salvage classification was only available at the study level and not by treatment arm; therefore, they could not be extracted for the BU-based conditioning regimen only.

Efficacy

Efficacy endpoints were extracted from the 38 publications that met the inclusion/exclusion criteria and reported the use of BU-based conditioning regimens for patients with MM undergoing auto-SCT. Most of the studies included a mixed patient population of patients who were newly diagnosed as well as those who had relapsed. Sample size-weighted averages were used for the aggregated efficacy and safety endpoints.

Response Rates

The criteria used to evaluate response varied amongst the studies; however, the European Group for Blood and Bone Marrow Transplant/International Bone Marrow Transplant Registry/American Bone Marrow Transplant Registry criteria were primarily used. Of all the studies using BU-based condi-

tioning regimens in which response rates were reported (29 out of 38 studies), the weighted average CR rate was 38% (range: 8%–100%) and the weighted average PR rate was 45% (range: 0%–72%). With the BU-MEL regimen, the weighted average CR rate was 47% (range: 17%–100%) and the weighted average PR rate was 42% (range: 0%–59%) (Table 1).

In publications that included only patients considered for an upfront auto-SCT, BU-based conditioning regimens led to a weighted average CR rate of 39% (range: 8%–79%) and a weighted average PR rate of 45% (range: 7%–72%), whereas patients who had undergone a salvage auto-SCT achieved a weighted average CR rate of 34% (range: 17%–73%) and a weighted average PR rate of 39% (range: 15%–67%).

Progression and Overall Survival Data

In studies where survival data were reported (17 out of 38 studies), the use of BU-based conditioning regimens resulted in a weighted average OS of 56 months (range: 8–126 months) and a weighted average PFS of 31 months (range: 14–121 months). In studies including only the BU-MEL conditioning regimen, the weighted average OS was 70 months (range: 57–126 months) and the weighted average PFS was 46 months

Table 1. Response rates after busulfan-based conditioning regimens in transplant-eligible patients with multiple myeloma undergoing autologous stem cell transplantation

Study	Sample size (n)	Regimen	Upfront (n)	Salvage (n)	Median follow-up period, mos (range)	Partial response (%)	Complete response (%)	Median PFS time (mos)	Median OS time (mos)
Lahuerta et al. [18]	225	BU-MEL (oral)	225	0	72	39	51	41	79
Ria et al. [19]	14	BU-MEL (oral)	14	0		7.1	78.6	121	126
Lahuerta et al. [20]	186	BU-MEL (oral)	148	38			51		57
	28	BU-CY (oral)							39
Clark et al. [21]	26	BU-MEL (oral)	26	0	36 (6–63)	46	54	48	60
Lemoli et al. [22]	47	BU-MEL (oral)	0	47	28 (2–53)				
Kebriaei et al. [23]	41	BU-MEL (i.v.)	0	41	38 (3–57)	39	17		
Alegre et al. [24]	24	BU-MEL (oral)	15	9	20 (4–34)	38	58		
Blanes et al. [25]	55	BU-MEL (i.v.)	49	6	15	38	49		
Tribalto et al. [26]	39	BU-MEL (oral)	39	0	55	59	41		57
Cavo et al. [27]	158	BU-MEL (oral)	158	0	75		47		71
Capria et al. [28]	32	Idarubicin-BU-MEL (oral)	32	0					
Meloni et al. [29]	28	Idarubicin-BU-MEL (oral)	18	10	20 (12–36)	12	40		
Reece et al. [30]	14	BU-CY-MEL (oral)			20 (6–42)	7.1	21		
Bensinger et al. [31]	63	BU-CY ± TBI and BU-MEL-Thiotepa (oral)	6	57	31.2	48	40		
Talamo et al. [32]	79	BU-CY (oral and i.v.)	60	19	41 (2–132)	60.7	25.3	20	45
Toor et al. [33]	104	BU-CY (oral)	74	30	26 (2–98)			26	57
Schiller et al. [34]	55	BU-CY (oral)	55	0	33 (7–44)	72	8	14	20
Huijgens et al. [35]	49	BU-CY (oral)	25	24					61
Ballester et al. [36]	6	BU-CY (oral)	6	0	(6–39)	50	33.3		
Shimoni et al. [37]	120	BU-CY-thiotepa (oral)	43	77	29 (7–90)	55	26		38
Giralt et al. [38]	14	BU-CY-thiotepa (oral)	2	12		18	9		
Dimopoulos et al. [39]	40	BU-CY-thiotepa (oral)	13	27					
Anagnostopoulos et al. [40]	97	BU-CY-thiotepa (oral)	97	0		50	16	21	46
Brinker et al. [41]	54	BU-CY-etoposide (oral)	54	0	44 (6.6–138)	19	15		
Cogle et al. [42]	26	BU-CY-etoposide (oral)	19	7	30 (9–59)		38		43
Benson et al. [11]	62	BU-CY-etoposide (oral)	56	6		53	24	26.7	31.2
Reynolds et al. [43]	35	BU-CY-TBI (oral)	0	35	24				
Einsele et al. [44]	89	BU-CY-TBI (oral)	33	56	56 (21–76)	56	44		61
Mansi et al. [45]	15	BU (oral)	0	15		15	31		8

Abbreviations: BU, busulfan; CY, cyclophosphamide; MEL, melphalan; OS, overall survival; PFS, progression-free survival; PR, partial response; TBI, total body irradiation.

(range: 41–121 months; Table 1). In publications that included only patients considered for an upfront auto-SCT, the weighted average OS was 66 months (range: 20–126 months) and the weighted average PFS was 35 months (range: 14–121 months) with the use of BU-based conditioning regimens.

Among the selected publications, the most commonly used conditioning regimen was BU-MEL. The BU-MEL regimen was used in 15 of the publications and a total of 928 patients were treated with this conditioning regimen. Three of these studies compared BU-MEL with MEL in patients considered for auto-SCT [18–20]. Results of studies comparing BU-MEL with MEL are summarized in Table 2.

In a retrospective analysis of the Spanish registry, Lahuerta et al. compared the outcomes of 821 patients with MM treated with different conditioning regimens prior to transplantation [20]. Conditioning regimens included MEL200 ($n = 472$), MEL140 with total body irradiation ($n = 135$), BU-MEL ($n = 186$), and BU-cyclophosphamide ($n = 28$). The authors

reported a significantly higher CR rate in the BU-MEL arm compared with the MEL200 and MEL140 plus total body irradiation arms (51% vs. 45% vs. 31%; $p = .007$). The median event-free survival and OS times for BU-MEL were 30 and 57 months compared with 22 and 46 months for MEL200; however, differences between groups did not reach statistical significance. There was also no significant difference in TRM between the MEL200 and BU-MEL arms (4% vs. 6%; $p = .2$).

A second study by Ria et al. was a nonrandomized controlled study of 30 patients who were low risk and untreated with stage III MM [19]. A total of 16 patients received MEL and 14 patients received BU-MEL as a conditioning regimen prior to transplantation. The overall response rate (ORR) was significantly higher in the BU-MEL arm than in the MEL arm (85% vs. 75%; $p < .05$). No differences in median OS times between groups were demonstrated (126 months for BU-MEL vs. 108 months for MEL; $p = .7$). There was no significant difference in TRM, hospitalization time, or toxicity between the two study arms.

Table 2. Efficacy endpoints in studies comparing melphalan with busulfan-melphalan as a conditioning regimen for patients with multiple myeloma undergoing autologous stem cell transplantation

Study	Melphalan					Busulfan-melphalan				
	Sample size (n)	CR (%)	PR (%)	Median PFS (mos)	Median OS (mos)	Sample size (n)	CR (%)	PR (%)	Median PFS (mos)	Median OS (ms)
Lahuerta et al. [18]	542	53 ^a	39	31	71	225	51 ^a	39	41	79
Ria et al. [19]	16	38	38	97	108	14	79	7	121	126
Lahuerta et al. [20]	472	45	45	22 ^b	46	186	51	44	30 ^b	57
Total/mean	1,030	49	42	28	60	425	52	40	39	71

^aIncludes complete response and near complete response.

^bEvent-free survival.

Abbreviations: CR, complete response; OS, overall survival; PFS, progression-free survival; PR, partial response.

In a more recent study from the Spanish Myeloma Working Group, Lahuerta et al. reported the results of a large non-randomized trial comparing BU-MEL ($n = 225$) and MEL ($n = 542$) [18]. Following transplantation, the CR rate was similar in the two arms (BU-MEL: CR = 38%, nCR = 13%; MEL: CR = 36%, nCR = 17%). There was a significantly longer PFS time in the BU-MEL arm (41 months) compared with the MEL arm (31 months; $p = .009$), although the OS data were similar between the two arms (79 months for BU-MEL vs. 71 months for MEL). However, access to novel agents as salvage therapy after relapse or progression was significantly lower for patients receiving BU-MEL (43%) than for those receiving MEL (58%; $p = .01$). The authors reported a significantly higher TRM rate in the BU-MEL arm (8.4%) compared with the MEL arm (3.5%; $p = .002$). This difference was mainly attributable to a significantly higher incidence of veno-occlusive disease (VOD) with oral BU (8% in the BU-MEL arm vs. 0.4% in the MEL arm; $p < .00001$). Although a higher incidence of VOD has been observed with oral BU, the safety profile of BU-MEL has been significantly improved with the introduction of an i.v. BU formulation. Intravenous BU is easier to administer and eliminates first-pass metabolism through the liver, reducing toxicity to the liver [25].

Finally, a recent analysis was performed comparing patients undergoing one auto-SCT after i.v. BU-MEL ($n = 51$) with a group given MEL alone with a planned second (tandem) auto-SCT if a CR was not achieved ($n = 102$). CR/nCR was achieved in 51% of patients in each group. After median follow-up times of 32 and 40.5 months in the BU-MEL group and the control group, respectively, the median PFS time was 37.6 months for patients who received BU-MEL and 26.5 months for those in the control group. The OS rate at 4 years was 65% and 62% in the two groups, but this was not significant. TRM was 4% with BU-MEL compared with 5% in the tandem transplant control arm [46].

Safety

Safety endpoints were extracted from the 38 publications that met the inclusion/exclusion criteria. They reported the use of BU-based conditioning regimens for patients with MM who were eligible for transplant undergoing auto-SCT.

The sample size-weighted mean TRM rate was 7.0% (range: 0–29%) and the most common cause of death was VOD. Two recent trials using i.v. BU-based conditioning have reported a TRM rate of 3.6% [25] and 1% [23] and an incidence

of fatal VOD of 0% [25, 23]. The 1% TRM rate reported by Kebriaei et al. [23] does not distinguish between patients with Hodgkin lymphoma, non-Hodgkin lymphoma, and MM who were included in the study.

A total of 1,512 patients were evaluable for safety. Table 3 reports the most common AEs of any severity (grades 0–4) associated with BU-based conditioning regimens for patients with MM who were eligible for transplant undergoing auto-SCT. Table 4 reports the most commonly reported severe AEs (grade 3–4) associated with BU-based conditioning regimens in this population.

DISCUSSION

Opportunities to improve outcomes in MM exist at all points of the auto-SCT treatment algorithm, including the induction, conditioning, and consolidation/maintenance treatment stages. However, despite improvements in induction and maintenance regimens, few studies have examined strategies to improve pretransplant conditioning regimens. In an effort to improve such conditioning regimens, the addition of BU to standard regimens has been examined in a number of clinical trials. This article examined the addition of BU to standard regimens through a systematic literature review.

A single MEL-based auto-SCT following older induction regimens typically produces a CR in 20%–40% of patients and a median PFS time of 2.5–4 years [10]. Outcomes using BU-based conditioning regimens compare favorably; the results of this literature review show they yield CR rates of approximately 38% and an average PFS time of 2.6 years. BU-MEL was also the most commonly administered BU-based conditioning regimen. The results observed with BU-MEL appear to be even better, with CR rates improving to 47% with an average PFS time of 3.8 years. Given these improvements in efficacy, BU-MEL may therefore be the treatment of choice amongst the BU-based conditioning regimens.

To further examine the benefits of adding BU to MEL, three studies compared BU-MEL with MEL as pretransplant conditioning (Table 2) [18–20]. Although these were not randomized comparisons, the overall ORRs—including CR and PR—were consistently higher for BU-MEL than MEL; in most cases, the differences were statistically significant. The PFS and OS rates also favored BU-MEL over MEL, although the differences did not always reach statistical significance. Although an increase in VOD has been observed with oral BU, the i.v. formulation appears to

Table 3. Commonly reported adverse events of all grades in 1,512 transplant-eligible patients with multiple myeloma receiving busulfan-containing conditioning regimens prior to autologous stem cell transplantation

Adverse event (grade 0–4)	No. of patients	Rate (%)
Infections	695	46
Mucocitis and stomatitis	585	39
Gastrointestinal toxicity	444	29
Hepatic toxicity	292	19
Pulmonary toxicity	208	14
Cardiac toxicity/cardiac dysrhythmia	203	13
Central nervous system/neurotoxicity	194	13
Renal toxicity	109	7
Bladder toxicity	104	7
Febrile neutropenia	93	6
Hemorrhage	92	6
Allergy	89	6

Table 4. Grade 3–4 adverse events reported in 1,512 transplant-eligible patients with multiple myeloma receiving busulfan-containing conditioning regimens prior to autologous stem cell transplantation

Adverse event (grade 3–4)	No. of patients	Rate (%)
Mucocitis and stomatitis	253	17
Infections	79	5
Gastrointestinal toxicity	63	4
Pain	37	2
Hepatic toxicity	34	2
Septicemia	10	0.7
Pulmonary toxicity	6	0.4
Hemorrhage	3	0.2
Hemorrhagic cystitis	3	0.2
Neurotoxicity	3	0.2
Renal toxicity	3	0.2
Bladder toxicity	2	0.1
Dyspnea	2	0.1
Renal and bladder toxicity	2	0.1

reduce the risk of this toxicity. Given the improvements in outcomes with the addition of BU to MEL, the BU-MEL conditioning regimen—using i.v. BU—may be a useful strategy to enhance auto-SCT outcomes in patients with MM.

An interesting finding of the studies examining the efficacy of BU-MEL is that improvements in PFS and OS times were observed even when response rates were similar to standard MEL conditioning regimens (Table 2). Almost all previous auto-SCT studies demonstrate a correlation between a patient's quality of response to treatment—in particular the achievement of a durable CR—and improved PFS and OS times [47]. As discussed, however, a case-matched Spanish study showed that despite an identical CR/nCR rate of 51% in each arm, a single transplant following BU-MEL conditioning yielded a longer PFS time than the tandem arm. This outcome raises the possi-

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bility that a single transplant with double-alkylating agent conditioning may be more efficient than a tandem transplant following high-dose MEL alone [46]. One possible explanation for the discrepancy between the depth of response and PFS and OS times is that BU may alter the bone marrow microenvironment in a manner that is unfavorable to the tumor cells, in addition to effecting direct myeloma cell cytotoxicity. Therefore, malignant proliferation might be reduced but not eliminated [48, 49]. Another aspect of this observation may relate either to the limitations of the current methods for defining response or the variations in criteria used by different groups to try to assess the tumor burden in myeloma. For instance, CR, nCR, and VGPR, which are based on different levels of residual monoclonal protein, have all been correlated with a better outcome [47]. More useful information may become available with the introduction of more sensitive measurements of residual tumor.

Recently, posttransplant assessment of MRD in the marrow has been evaluated by both molecular techniques, such as polymerase chain reaction and multiparameter flow cytometry immunophenotyping [9, 47]. The assessment of MRD, although standard in many other hematologic malignancies, is still considered to be investigational in MM; however, early reports have yielded encouraging results. One study from the Spanish group has demonstrated the clinical significance of MRD, as patients who were MRD-negative by multiparameter flow cytometry but who remained immunofixation-positive had significantly longer PFS times compared with patients who were MRD-positive and immunofixation-negative [50]. A more recent report has confirmed the usefulness of MRD assessment in a much larger group of 1,221 patients with MM receiving either transplant or nontransplant MM therapies; the achievement of MRD-negativity in both groups of patients was highly predictive of PFS [51]. Therefore, use of MRD in the post-auto-SCT setting may be more reliable as a predictor of treatment outcome than older assessments of CR involving immunofixation. More information will become available regarding the role of MRD because several large ongoing cooperative group trials are including this parameter as part of the response determinations.

Another notable finding of this analysis was the 47-month (3.8-year) duration of response following BU-MEL conditioning. Maintenance strategies studied in myeloma include the use of thalidomide maintenance, which produces a PFS time of 28–34 months after MEL-based transplants [5, 52]. Lenalidomide maintenance has produced even more striking results: two recent randomized studies reported PFS times of 41 and 46 months (3.4 and 3.8 years) when lenalidomide is com-

menced 2–3 months after high-dose MEL conditioning and auto-SCT and continued until disease progression [6, 14]. Given these reported outcomes, one could speculate either that BU-MEL might avoid the cost and toxicity of lenalidomide while ensuring a relatively long PFS, or that the addition of lenalidomide maintenance after BU-MEL might produce even longer periods of disease control. Obviously, these possibilities would have to be assessed in prospective trials designed to evaluate each hypothesis before firm conclusions can be made.

In addition, future studies using the more modern assays of response discussed earlier may help elucidate the improvements in outcomes seen with the BU-MEL conditioning regimen. Assessments such as MRD may also help in determining the role of post-auto-SCT measures—such as consolidation and/or maintenance therapy—after more effective conditioning regimens such as BU-MEL.

CONCLUSIONS

To optimize outcomes in MM, a growing body of evidence indicates that improving conditioning regimens given before transplantation is vital; however, little research has been conducted in this area. Intensifying conditioning regimens with the addition of BU shows improved efficacy and a good safety profile, with BU-MEL being the most commonly used BU-based combination. The BU-MEL regimen has shown superior efficacy when compared with other regimens and has a satisfactory safety profile, particularly when the i.v. formulation of BU is used. A review of the available data suggests that further clinical trials to examine the efficacy of BU-MEL conditioning, following induction with novel agents, is warranted. To further evaluate and capture the full depth of response of conditioning regimens, clinical endpoints and their definition need to be refined, along

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with the incorporation of sensitive techniques into clinical trials to more accurately evaluate CR and/or MRD.

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DISCLOSURES

Donna Reece: Otsuka (H, RF); **Richard LeBlanc:** Celgene (C/A); Celgene, Janssen, The Binding Site (RF); **Khalid Mezzi:** Otsuka (E); **Andrew Belch:** Janssen, Celgene (RF). The other authors indicated no financial relationships.

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REFERENCES

- Berenson JR, Lichtenstein A, Porter L et al. Long-term pamidronate treatment of advanced multiple myeloma patients reduces skeletal events. *Myeloma Aredia Study Group. J Clin Oncol* 1998;16:593–602.
- Turesson I, Velez R, Kristinsson SY et al. Patterns of multiple myeloma during the past 5 decades: Stable incidence rates for all age groups in the population but rapidly changing age distribution in the clinic. *Mayo Clin Proc* 2010;85:225–230.
- Canadian Cancer Society's Steering Committee on Cancer Statistics. *Canadian Cancer Statistics* 2012. Toronto, ON: Canadian Cancer Society, 2012.
- Djulfegovic B, Kumar A. Multiple myeloma: Detecting the effects of new treatments. *Lancet* 2008;371:1642–1644.
- Lokhorst H, van der Holt B, Zweegman S 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;115:1113–1120.
- McCarthy PL, Owzar K, Hofmeister CC et al. Lenalidomide after stem-cell transplantation for multiple myeloma. *N Engl J Med* 2012;366:1770–1781.
- van de Velde HJ, Liu X, Chen G et al. Complete response correlates with long-term survival and progression-free survival in high-dose therapy in multiple myeloma. *Haematologica* 2007;92:1399–1406.
- Martinez-Lopez J, Blade J, Mateos MV et al. Long-term prognostic significance of response in multiple myeloma after stem cell transplantation. *Blood* 2011;118:529–534.
- Paiva B, Martinez-Lopez J, Vidriales MB et al. Comparison of immunofixation, serum free light chain, and immunophenotyping for response evaluation and prognostication in multiple myeloma. *J Clin Oncol* 2011;29:1627–1633.
- Reece DE. Management of multiple myeloma: The changing landscape. *Blood Rev* 2007;21:301–314.
- Benson DM Jr, Elder PJ, Lin TS et al. High-dose melphalan versus busulfan, cyclophosphamide, and etoposide as preparative regimens for autologous stem cell transplantation in patients with multiple myeloma. *Leuk Res* 2007;31:1069–1075.
- Attal M, Harousseau JL, Leyvraz S. Maintenance therapy with thalidomide improves survival in patients with multiple myeloma. *Haematologica* 2011;96(Suppl 1):S23.
- Ludwig H, Durie BG, McCarthy P et al. IMWG consensus on maintenance therapy in multiple myeloma. *Blood* 2012;119:3003–3015.
- Attal M, Lauwers VC, Marit G et al. Lenalidomide maintenance after stem-cell transplantation for multiple myeloma. *N Engl J Med* 2012;366:1782–1791.
- Roussel M, Moreau P, Huynh A et al. Bortezomib and high-dose melphalan as conditioning regimen before autologous stem cell transplantation in patients with de novo multiple myeloma: A phase 2 study of the Intergroupe Francophone du Myelome (IFM). *Blood* 2010;115:32–37.
- Otsuka Pharmaceutical Co. Ltd. *Product Monograph: Busulfex (Busulfan)*. July 27, 2011.
- Thakkar K, Boatright RO, Gilger MA et al. Gastroesophageal reflux and asthma in children: A systematic review. *Pediatrics* 2010;125:e925–e930.
- Lahuerta JJ, Mateos MV, Martinez-Lopez J et al. Busulfan 12 mg/kg plus melphalan 140 mg/m² versus melphalan 200 mg/m² as conditioning regimens for autologous transplantation in newly diagnosed multiple myeloma patients included in the PETHEMA/GEM2000 study. *Haematologica* 2010;95:1913–1920.
- Ria R, Falzetti F, Ballanti S et al. Melphalan versus melphalan plus busulfan in conditioning to autologous stem cell transplantation for low-risk multiple myeloma. *Hematol J* 2004;5:118–122.
- Lahuerta JJ, Grande C, Blade J et al. Myeloablative treatments for multiple myeloma: Update of a comparative study of different regimens used in patients from the Spanish registry for transplantation

in multiple myeloma. *Leuk Lymphoma* 2002;43:67–74.

21. Clark AD, Douglas KW, Mitchell LD et al. Dose escalation therapy in previously untreated patients with multiple myeloma following Z-Dex induction treatment. *Br J Haematol* 2002;117:605–612.

22. Lemoli RM, Martinelli G, Zamagni E et al. Engraftment, clinical, and molecular follow-up of patients with multiple myeloma who were reinfused with highly purified CD34+ cells to support single or tandem high-dose chemotherapy. *Blood* 2000;95:2234–2239.

23. Kebriaei P, Madden T, Kazerooni R et al. Intravenous busulfan plus melphalan is a highly effective, well-tolerated preparative regimen for autologous stem cell transplantation in patients with advanced lymphoid malignancies. *Biol Blood Marrow Transplant* 2011;17:412–420.

24. Alegre A, Lamana M, Arranz R et al. Busulfan and melphalan as conditioning regimen for autologous peripheral blood stem cell transplantation in multiple myeloma. *Br J Haematol* 1995;91:380–386.

25. Blanes M, de la Rubia J, Lahuerta JJ et al. Single daily dose of intravenous busulfan and melphalan as a conditioning regimen for patients with multiple myeloma undergoing autologous stem cell transplantation: A phase II trial. *Leuk Lymphoma* 2009;50:216–222.

26. Tribalto M, Amadori S, Cudillo L et al. Autologous peripheral blood stem cell transplantation as first line treatment of multiple myeloma: An Italian multicenter study. *Haematologica* 2000;85:52–58.

27. Cavo M, Tosi P, Zamagni E et al. Prospective, randomized study of single compared with double autologous stem-cell transplantation for multiple myeloma: Bologna 96 clinical study. *J Clin Oncol* 2007;25:2434–2441.

28. Capria S, Petrucci MT, Pulsoni A et al. High-dose idarubicin, busulfan and melphalan for autologous stem cell transplantation in multiple myeloma responsive to DAV chemotherapy: Comparison with a historical control. *Acta Haematol* 2006;115:9–14.

29. Meloni G, Capria S, Trasarti S et al. High-dose idarubicin, busulfan and melphalan as conditioning for autologous blood stem cell transplantation in multiple myeloma. A feasibility study. *Bone Marrow Transplant* 2000;26:1045–1049.

30. Reece DE, Barnett MJ, Connors JM et al. Treatment of multiple myeloma with intensive chemotherapy followed by autologous BMT using marrow purged with 4-hydroperoxycyclophosphamide. *Bone Marrow Transplant* 1993;11:139–146.

31. Bensinger WI, Rowley SD, Demirer T et al. High-dose therapy followed by autologous hematopoietic stem-cell infusion for patients with multiple myeloma. *J Clin Oncol* 1996;14:1447–1456.

32. Talamo G, Claxton DF, Dougherty DW et al. BU and CY as conditioning regimen for autologous transplant in patients with multiple myeloma. *Bone Marrow Transplant* 2009;44:157–161.

33. Toor AA, Ayers J, Strupek J et al. Favourable results with a single autologous stem cell transplant following conditioning with busulphan and cyclophosphamide in patients with multiple myeloma. *Br J Haematol* 2004;124:769–776.

34. Schiller G, Vescio R, Freytes C et al. Autologous CD34-selected blood progenitor cell transplants for patients with advanced multiple myeloma. *Bone Marrow Transplant* 1998;21:141–145.

35. Huijgens PC, Dekker-Van Roessel HM, Jonkhoff AR et al. High-dose melphalan with G-CSF-stimulated whole blood rescue followed by stem cell harvesting and busulphan/cyclophosphamide with autologous stem cell transplantation in multiple myeloma. *Bone Marrow Transplant* 2001;27:925–931.

36. Ballester OF, Tummala R, Janssen WE et al. High-dose chemotherapy and autologous peripheral blood stem cell transplantation in patients with multiple myeloma and renal insufficiency. *Bone Marrow Transplant* 1997;20:653–656.

37. Shimoni A, Smith TL, Aleman A et al. Thiotepa, busulfan, cyclophosphamide (TBC) and autologous hematopoietic transplantation: An intensive regimen for the treatment of multiple myeloma. *Bone Marrow Transplant* 2001;27:821–828.

38. Giral S, Weber D, Colome M et al. Phase I trial of cyclosporine-induced autologous graft-versus-host disease in patients with multiple myeloma undergoing high-dose chemotherapy with autologous stem-cell rescue. *J Clin Oncol* 1997;15:667–673.

39. Dimopoulos MA, Alexanian R, Przepiorka D et al. Thiotepa, busulfan, and cyclophosphamide: A new preparative regimen for autologous marrow or blood stem cell transplantation in high-risk multiple myeloma. *Blood* 1993;82:2324–2328.

40. Anagnostopoulos A, Aleman A, Ayers G et al. Comparison of high-dose melphalan with a more intensive regimen of thiotepa, busulfan, and cyclophosphamide for patients with multiple myeloma. *Cancer* 2004;100:2607–2612.

41. Brinker BT, Waller EK, Leong T et al. Maintenance therapy with thalidomide improves overall survival after autologous hematopoietic progenitor cell transplantation for multiple myeloma. *Cancer* 2006;106:2171–2180.

42. Cogle CR, Moreb JS, Leather HL et al. Busulfan,

cyclophosphamide, and etoposide as conditioning for autologous stem cell transplantation in multiple myeloma. *Am J Hematol* 2003;73:169–175.

43. Reynolds C, Ratanatharathorn V, Adams P et al. Allogeneic stem cell transplantation reduces disease progression compared to autologous transplantation in patients with multiple myeloma. *Bone Marrow Transplant* 2001;27:801–807.

44. Einsele H, Bamberg M, Budach W et al. A new conditioning regimen involving total marrow irradiation, busulfan and cyclophosphamide followed by autologous PBST in patients with advanced multiple myeloma. *Bone Marrow Transplant* 2003;32:593–599.

45. Mansi J, da Costa F, Viner C et al. High-dose busulfan in patients with myeloma. *J Clin Oncol* 1992;10:1569–1573.

46. Blanes M, De La Rubia J, Lahuerta J et al. Outcomes in patients with multiple myeloma following autologous stem cell transplantation using intravenous busulfan and melphalan: A matched comparison to a double autologous transplant strategy. *Blood* 2010;116:3560.

47. Chanan-Khan AA, Giral S. Importance of achieving a complete response in multiple myeloma, and the impact of novel agents. *J Clin Oncol* 2010;28:2612–2624.

48. Zocchi MR, Poggi A. Targeting the microenvironment in hematological malignancies: How to condition both stromal and effector cells to overcome cancer spreading. *Curr Med Chem* 2011;18:5172–5173.

49. Hayun M, Saida H, Albeck M et al. Induction therapy in a multiple myeloma mouse model using a combination of AS101 and melphalan, and the activity of AS101 in a tumor microenvironment model. *Exp Hematol* 2009;37:593–603.

50. Paiva B, Vidriales MB, Cervero J et al. 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.

51. Rawstron AC, de Tute RM, Child A et al. Minimal residual disease (MRD) assessment using multiparameter flow cytometry (MFC) predicts outcomes in both intensively and non-intensively treated patients: Results from the MRC Myeloma IX trial. *Haematologica* 2011;96(Suppl 1):30–31.

52. Stewart A, Trudel S, Bahlis N et al. A randomized phase III trial of thalidomide and prednisone as maintenance therapy following autologous stem cell transplantation (ASCT) in patients with multiple myeloma (MM): The NCIC CTG MY.10 Trial. *Blood* 2010;116:39.