The Choice of Multiple Myeloma Induction Therapy Affects the Frequency and Severity of Oral Mucositis After Melphalan-Based Autologous Stem Cell Transplantation

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Abstract

Mucositis is a significant complication of high dose melphalan autologous transplantation (AHSCT) for myeloma. We hypothesized that prior therapy received would impact on mucositis risk in AHSCT. We retrospectively analyzed 128 sequential 200mg/m2 melphalan AHSCT performed as part of primary. There was a significant reduction in mucositis risk in patients receiving immunomodulator based induction therapy compared to conventional chemotherapy.

Introduction/Background: Mucositis is a common complication of high-dose melphalan (HDM) used before autologous stem cell transplantation (ASCT) for multiple myeloma (MM). Mucositis rates are influenced by previous chemotherapy (CT) exposure. We examined the effect of induction therapy before ASCT on ASCT mucositis rates. **Patients and Methods:** Patients undergoing first 200 mg/m^2 HDM ASCT were assessed. Those receiving < 200 mg/m^2, or those with previous ASCT were excluded. Patients were evaluated depending on type of induction therapy (CT, immunomodulatory drug [IMiD], or proteasome inhibitor [PI]) before ASCT. A case record review was performed and data collected on response to induction, rates of Grade 3/4 mucositis, and days of total parenteral nutrition (TPN) or parenteral opiate analgesia. **Results:** One hundred twenty-eight patients with ASCT were assessed. Induction therapy was CT- (n = 62), IMiD- (n = 51), or PI-based (n = 15) therapy. Patient characteristics were overall similar, including median age, MM stage, and CD34$^+$ cell dose. IMiD-based therapy patients had lower rates of mucositis (33% vs. 53%; $P = .03$) and less opiate requirements (10% vs. 31%; $P = .02$) compared with those treated with CT. Rates of mucositis and opiate use in the PI group were not different to the CT cohorts (33% vs. 53%; $P = .6$ and 13% vs. 31%; $P = .13$), likely due to concurrent anthracycline exposure. TPN usage was similar (CT, 42%; IMiD, 35%; and PI, 20%), as was neutropenia duration and antibiotic usage. **Conclusion:** Patients treated with IMiD-based regimens before HDM ASCT had significantly lower rates of mucositis than those treated with CT-based therapy. There were too few patients who received PI therapy to evaluate the effect.

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Introduction

Oral mucositis is a common complication of autologous stem cell transplantation (ASCT), with rates of severe (Grade 3 or 4) mucositis according to the Common Terminology Criteria for Adverse Events (CTCAE) reported to be as high as 46%.[1] In patients with multiple myeloma (MM) undergoing ASCT the overall rate of mucositis has been reported as 75%, with severe mucositis recorded in 21%, with melphalan dose and renal impairment before transplant identified as risk factors for mucositis severity.[2] Preexisting oral pathology, the presence of oral appliances, dental hygiene, and previous oral lesions have also been identified as risk factors for mucositis.[3]

Patients with severe mucositis have a significantly greater rate and duration of neutropenic sepsis.[1,4] Furthermore, more than 40% of

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patients undergoing ASCT will report mucositis as their most debilitating transplantation-related side effect.[5] Severity of mucositis is identified as a major risk factor for transplant-associated mortality in autologous and allogeneic transplantation.[4]

Severe mucositis forms 1 of the major barriers to outpatient-based ASCT procedures in MM. Supportive care for severe mucositis including intravenous opiates, enteral feeding, and total parenteral nutrition (TPN) are difficult or impossible to administer in the outpatient setting, and mucositis-associated complications such as neutropenic sepsis also necessitate readmission. In a study of outpatient-based melphalan-conditioned ASCT in MM, a readmission rate of 36% (10 of 28 patients) was observed, of which half were for severe mucositis.[6] In less well selected patients, the readmission rate might be significantly greater.[7]

Since the mid 1990s, high-dose chemotherapy (CT) with ASCT has been a key part of consolidation for patients with MM after conventional CT-based induction (CCT). ASCT delivers deeper MM responses and is associated with improved progression-free and overall survival.[8-10] Historically, the most commonly used CT regimen was VAD (vincristine 1.6 mg, adriamycin 36 mg/m^2, and dexamethasone 40 mg daily for 4 days).[11,12] Novel therapy-based induction with either immunomodulatory drug (IMiD) or proteasome inhibitor (PI) therapy provide superior outcomes compared with CT-based induction.[13-18] Although there is interest in therapeutic approaches that defer transplantation until first disease progression, with ongoing trials continuing in this area,[19] current evidence supports ASCT after primary induction therapy as the standard of care among transplant-eligible patients.[20]

Because CT might be associated with subclinical mucosal lesions,[21] we hypothesized that the type of previous induction therapy might influence the incidence and severity of ASCT-related mucositis. We investigated the effect of induction therapy before transplantation on mucositis in patients undergoing ASCT for MM at our institution.

Patients and Methods

We undertook a retrospective review of case records of patients who had received ASCT for MM at the Peter MacCallum Cancer Centre between May 2005 and August 2011. All data were collected in accordance with approval from an institutional ethics committee.

Patients were considered evaluable if they were undergoing a first 200 mg/m^2 melphalan ASCT for treatment of MM, with those receiving subsequent ASCT or salvage therapy excluded. Also excluded were patients who had not received any induction therapy or only steroids before ASCT.

Data were collected on demographic information, previous therapies received, and MM status including stage at diagnosis.[22] Treatment data including regimen received, steroid dose, and time from therapy to transplant were determined from clinical notes, pharmacy records, and treatment summaries. ASCT data were obtained on the conditioning regimen received, stem cell dose received, rates of mucositis, onset of fever, and day of discharge from day of stem cell infusion. Clinically significant mucositis was defined as Grade 3 or 4 clinical mucositis according to the CTCAE version 3.0.[23] Surrogate measures of mucositis were also measured including parenteral opiate use and the use of TPN. Response to therapy was categorized according to the International Uniform Response Criteria.[24]

Patients were evaluated on the basis of induction therapy received; either CT-, IMiD-, or PI-based therapy. Any patient who had received a CT-based treatment was classified as having received CT irrespective of any subsequent novel agent exposure before transplantation, and those who received a single CT agent in combination with either IMiD or PI therapy were counted in their respective groups.

Data analysis was performed using the R statistical platform version 2.14.1 (R Foundation for Statistical Computing, Vienna, Austria), using the χ^2 test and Fisher exact test for comparison of nominative data and the Kruskal-Wallis test for analysis of nonparametric data. Secondary evaluation was performed on the basis of steroid exposure, time between treatment, and ASCT and anthracycline exposure to establish which, if any, of these variables contributed to mucositis outcomes.

Results

A total of 128 sequential patients treated with 200 mg/m^2 melphalan ASCT after primary induction therapy were evaluated across the review period. An additional 120 episodes were not evaluated because they formed part of salvage therapy in relapsed or refractory MM (n = 59), were a second ASCT as part of a tandem ASCT (n = 10), received less than 200 mg/m^2 of melphalan (n = 40), steroid-only induction (n = 5), non−melphalan-based transplant (n = 3), did not receive induction therapy before transplantation (n = 3), received a delayed ASCT not as part of primary therapy (n = 1), and insufficient information available (n = 1).

The median time to ASCT from initiation of systemic therapy was 181 (range, 79-628) days, with no significant difference in time to ASCT in any of the treatment groups or in relation to mucositis outcomes (P = .98 for Grade 3 or 4 mucositis).

Of the episodes evaluated, 51 occurred after an IMiD-based induction, 62 after a CT-based induction, and 15 after PI-based induction (Table 1). Ten of the CT patients had received some exposure to an IMiD in the lead-up to their ASCT. Patients across all 3 groups were similar in terms of age, renal function, stage of disease, and baseline paraprotein level (Table 2). All patients had received cyclophosphamide and granulocyte colony stimulating factor based stem cell mobilization, and the median CD34$^+$ cell dose received was similar.

Primary Outcome Measures

The overall rate of Grade 3 or greater mucositis was 43%, with 33 of 62 in the CT group (53%), 17 of 51 in the IMiD group (33%), and 5 in the PI group (33%). The difference of mucositis rates between the IMiD and CT groups was 20% (P = .03). There was no statistically significant difference between the PI and CT groups or the IMiD and PI groups. Parenteral opiates were used for treatment of mucositis in 21% of patients, with 20 in the CT group (31%), 5 in the IMiD group (10%), and 2 in the PI group (13%). Statistical significance was observed in the difference between the IMiD and CT groups (P = .02), but not between the PI and CT or PI and IMiD groups. The rate of TPN use (42% CT, 35% IMiD, 20% PI) was not significantly different between the groups (Table 3).

Secondary Outcome Measures

Neutropenic sepsis was frequent (85%, n = 109) after ASCT for the whole cohort, with no significant difference between any of