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CD34+ Selection and the Severity of Oropharyngeal Mucositis in Total Body Irradiation-Based Allogeneic Stem Cell Transplantation

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Abstract

Objective—To evaluate the impact of ex vivo T cell depleted (TCD) by CD34+ selection on the incidence and severity of Oropharyngeal mucositis (OM) in after myeloablative allogeneic stem cell transplant (allo-SCT) with total body irradiation (TBI) conditioning. This approach has the advantage of avoiding methotrexate for graft versus host disease (GVHD) prophylaxis.

Patients and Methods—We analyzed the incidence and severity of OM in a cohort of 105 consecutive patients who underwent CD34+ selected (PBSC (peripheral blood stem cells) from HLA identical siblings) allo-SCT with total body irradiation (TBI) conditioning. OM was graded by the World Health organization (WHO) and the Bearman Regimen Related Toxicity (RRT) Scales.

Results—The incidence of WHO grade 3–4 OM was 34.3%. There were no cases of grade 3–4 OM by the RRT scale. Significant correlation was found between the severity of OM and the use of intravenous (IV) narcotic medications ($r^2=0.15$, $p=0.004$), Total parenteral nutrition (TPN) ($r^2=0.68$, $p<0.001$) and hospital length of stay (LOS) ($r^2=0.12$, $p=0.01$).

Discussion—TBI-induced OM can inflict significant morbidity in the early transplant period and the incidence of WHO grade 3–4 OM can exceed 50% when methotrexate is used for GVHD prophylaxis. In the CD34+ selected setting, methotrexate is avoided and the incidence of WHO grade 3–4 OM, use of TPN, and need for narcotic analgesia appear to be lower than historic evidence from standard T-replete allogeneic transplantation.

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Authorship Contributions:

A.A, A.J.B. and M.B. designed the study; A.A, P.A., K.L., N.A.J. and M.B. collected data; A.A, P.A., P.D.C., N.A.D. and M.B. analyzed and interpreted the data; D.S., M.S., R.Q.L., K.L., N.A.D, S.I., A.J.B and M.B. performed CD34+ selection or took care of patients; A.A, P.A, N.A.D. and M.B. wrote the manuscript. All authors critically revised the manuscript.

Conclusion—We conclude that toxicity from OM is tolerable in CD34+ selected allo-SCT and should be prospectively measured in randomized trials comparing CD34+ selection versus T-replete transplantation.

Keywords

Oropharyngeal mucositis; T cell depleted transplantation; CD34 selection; Oral mucositis; Quality of life; Allogeneic; Stem Cell Transplant; methotrexate; total body irradiation

Introduction

Oropharyngeal mucositis (OM) is a serious complication that develops in the majority of patients undergoing myeloablative conditioning for allogeneic hematopoietic stem cell transplant (allo-SCT) leading to significant morbidity and prolonged hospitalizations.[1] OM is considered to be the single worst complication of myeloablative conditioning in patient-reported outcomes.[2] Presenting as oral lesions with severe pain, dysphagia/odynophagia and with increased risk of infections from mucosal erosions, OM significantly impacts patient quality of life in the early transplant period. The major risk factors associated with development of OM include myeloablative conditioning, radiotherapy, and use of methotrexate for GVHD prophylaxis.[3] Severe OM, as defined by World Health Organization (WHO) criteria, occurs in up to 75% of patients undergoing allo-SCT with myeloablative conditioning regimens.[4] The manifestations of OM severity range from mild oral erythema to severe oral ulcerations requiring intravenous infusion of narcotic analgesics, parenteral nutrition and possibly preventative intubation for airway protection.[5] Denudation of mucosal lining may also contribute to bacteremia and potentially delay recovery and hospital discharge.[6,7] To date, Palifermin, a human recombinant keratinocyte growth factor is the only agent approved by US food and drug administration (FDA) for prevention of OM in myeloablative transplantation. However, Palifermin is associated with significant additional costs in the peritransplant period.[8]

The incidence of WHO grade 3–4 OM after total body irradiation (TBI) based myeloablative conditioning has been reported to exceed 50% when methotrexate is used for graft versus host disease (GVHD) prophylaxis.[4,9] Methotrexate functions as an antimetabolite and antiproliferative agent, interrupting a variety of interactions involving endothelium, extracellular matrix, metalloproteinases, submucosal reactions and connective tissue.[10] The risk of mucositis induced by methotrexate may be further increased if the patient carries methyltetrahydrofolate reductase (MTHFR) 677 T allele.[11] Substitution of methotrexate by alternative agents such as mycophenolate or sirolimus significantly reduces the severity of OM.[4,12,13]

Immunomagnetic CD34+ selection of the graft, a method of *ex vivo* T cell depletion (TCD), is a highly effective strategy for reducing GVHD. The Miltenyi CliniMACS system for CD34+ selection is currently FDA-approved. Initial reports of CD34+ selection allo-SCT have focused on the benefits of reducing acute or chronic GVHD and improving GVHD-free survival.[14–17] By avoiding the administration of methotrexate, CD34+ selection could theoretically reduce the risk of OM. Goldberg, et al. have studied the impact of Palifermin in

reducing mucositis in a cohort of 251 patients, but only 11 had TCD with the Miltenyi CliniMACS system.[18] We conducted a single institution retrospective analysis of the severity and incidence of OM and its related outcomes in 105 consecutive recipients of TBI-based myeloablative CD34+-selected allo-SCT.

Patients and Methods

Study Design

This is a single institute retrospective study of 105 consecutive patients with hematologic malignancies undergoing myeloablative T-cell depleted hematopoietic cell transplant (TCD) HCT, from a 6/6 human leukocyte antigen (HLA) identical sibling at the Hematology Branch of the National Heart, Lung and Blood Institute at the National Institutes of Health between 2006 and 2014 on institutional review board-approved protocols (06-H-0248, 07-H-0136, 12-H-0028, 13-H0144). The trials were registered at www.clinicaltrials.gov [NCT00378534, NCT00467961, NCT01517035, NCT01866839]. Written informed consent, consistent with the Helsinki Declaration, was obtained from all patients and donors.

Transplantation Protocols

All subjects received a fully myeloablative conditioning regimen consisting of fludarabine (25mg/m²/day) from day -8 thru day -4, age-adapted fractionated TBI from day -7 thru day -4 followed by cyclophosphamide (60 mg/kg/day) on day -3 and day -2. TBI was delivered in 8 fractions at a total dose of 1200cGy with lung shielding to 600cGy for subjects <age 55 years and 400–600cGy for subjects ≥ age 55 years (21 % of subjects). None of the subjects received palifermin or intravenous methotrexate. On day 0, subjects received a Granulocyte Colony-Stimulating factor (G-CSF) mobilized peripheral blood stem cell product selected for CD34+ progenitors using the Miltenyi CliniMACS Plus system (Miltenyi Biotec Inc., Cambridge, MA) along with a planned T- lymphocyte dose ranging between 5 to 50 × 10⁴ CD3+/kg (resulting in a 3–4 log TCD graft). Low dose cyclosporine was administered until day 21. Low dose cyclosporine from day-6 to day+21 was used for GVHD prophylaxis. Supportive care did not change in this period. Regular oral hygiene was performed with mouthwashes, which did not change in the period of observation. Prophylaxis with systemic antibiotics for prevention of bacterial infection is not employed at our center.

Outcome endpoints

OM was graded from the start of transplant conditioning (day-8) until day +21. The peak grades of OM by WHO grading[19] and by the Bearman RRT scale[20] were recorded. Esophagitis was not scored for this study. The total duration of IV narcotic analgesia in days, duration of total TPN in days, and microbiologic data were also collected through the same period.

Statistical Analysis

Summary statistics such as sample proportions, medians, standard deviations, and 95% confidence intervals, were used to describe patient characteristics. Unpaired t-tests were used to compare groups. Statistical significance was considered when $p < 0.05$. All statistical analyses were performed using Prism 5.03 (GraphPad Software, Inc. La Jolla.

Results

Patient characteristics

The median age was 42 years. 78% received fully ablative transplants (1200cGy) while 22% received reduced intensity (400–600cGy) TBI. Patient and transplant characteristics are summarized in (Table 1). Differences between transplant protocols are summarized in supplementary Table 1. The median time to absolute neutrophil count recovery to $>500/\mu\text{L}$ was 12 days.

OM incidence and severity

WHO grade 2–4 was observed in 46.7% of subjects and WHO grade 3–4 in 34.3% of subjects. Bearman grade 1 was observed in 53.3%, grade 2 in 15.2% and grade 3–4 in 0%. Grading of OM by the WHO and Bearman scales were highly correlated ($r^2=0.48$, $P<0.0001$) (Figure 1).

Infections, Narcotic use, TPN and Hospital Length of Stay

92.3% of subjects had febrile neutropenia and 67.6% developed a documented bacterial blood stream infection. 59.1% required intermittent and 15.2% required continuous IV narcotics for oral mucositis pain. 34.3% required TPN and the median duration of TPN was 9 days. In our group of patients, OM severity was correlated with the use of IV narcotics ($r^2=0.15$, $P=0.004$), duration of TPN ($r^2=0.68$, $p<0.001$), and weakly correlated with duration of initial hospitalization ($r^2=0.12$, $p=0.01$) (Figure 3) but not with the occurrence of bacteremia.

Role of conditioning intensity

Subjects who received reduced intensity conditioning had significantly lower incidence and severity of mucositis (Figure 2) and associated outcomes (Table 2). Only one subject receiving 400–600cGy TBI had WHO grade 3 OM and none had grade 2 Bearman.

Discussion

We show that OM remains a problem in TBI-based myeloablative stem cell transplantation and is correlated with IV narcotic requirements, duration of TPN and prolonged hospital LOS. With CD34+ selection and 1200cGy (fully ablative) TBI-based conditioning, the peak incidence of WHO grade 3–4 OM was 43% but Bearman grade 3–4 OM was 0%; while the severity was even lower with reduced intensity conditioning.

While ours was an uncontrolled study, the rates of OM with CD34+ selection in our study compare favorably with TBI-based transplant regimens containing methotrexate. [9] [4] The incidence of WHO grades 2–4 OM was 46.7% which is lower than in the study by Langner, et al that reported WHO grade 2–4 OM incidence ranging from 60% to 86% in subjects who received or did not receive palifermin, respectively. [9] Incidence of WHO grade 3–4 OM in the same study ranged from 37 % to 53%, in subjects who received or did not receive palifermin, respectively. In a prospective study with a different OM grading system, Cutler et al, using full dose TBI at 1400 cGy, reported an incidence of moderate – severe OM of

92% in methotrexate arm as opposed to 64% in the non-methotrexate arm.[4] Reductions in OM by substituting methotrexate have recently been confirmed by a multicenter randomized trial of Tacrolimus/Sirolimus versus Tacrolimus/Methotrexate. Tacrolimus/Sirolimus did not impact GVHD free survival but OM was greatly reduced.[13] Taken together, these data suggest that avoidance of methotrexate by CD34+ selection is at least moderately effective in reducing the peak severity of OM.

It is notable that in our study, subjects did not receive palifermin, which is an N terminal truncated (N23KGF) version of recombinant human KGF-1, and currently the only FDA approved agent for treatment of OM. [21,1] Palifermin was first demonstrated to be efficacious for treatment of OM in the setting of autologous SCT with TBI based conditioning regimens. Since its first approval by FDA in 2004, studies have shown its efficacy in reducing the severity, the incidence, and the duration of OM grades 2–4, in the allogeneic transplant setting as well. However, its efficacy in non-TBI based myeloablative conditioning is controversial. [1,9,22] Palifermin does not offer a survival benefit and does not impact the incidence of acute or chronic GVHD. Another major drawback with the use of Palifermin is the cost associated with its use. Nooka et al reported additional costs of \$5,511 for myeloma and \$13,792 for lymphoma patients for preventing one day of patient controlled analgesia.[8] Others have justified Palifermin as being cost-neutral.[23] Palifermin use has been described in allo-HSCT.[9,24] Goldberg, et al. showed that palifermin significantly decreased the durations of TPN, patient controlled analgesia (PCA) and hospital LOS in patients who received a myeloablative TBI-based but not busulfan-based chemotherapy conditioning in TCD allo-SCT recipients.[18] This is so far the largest published experience with palifermin in allo-SCT and suggests that palifermin may offer incremental benefit even in TCD transplantation.

Our study also described the practical consequences related to OM severity such as narcotic or TPN utilization and hospital LOS. The mean duration of intermittent narcotic analgesia was 7.1 days (range: 0 – 21 days) and 62 patients (59.1%) required intermittent narcotic analgesia. These results are comparable to a prospective randomized trial by Bolwell et al, who reported that 94% patients in the methotrexate arm received narcotic analgesics for an average of 15.5 days and 75% patients in the methotrexate-free arm received narcotic analgesics with an average of 9.5 days. [12] Another prospective randomized study by Langner et al reported average narcotic analgesia duration of 7 days. [9] 36 patients (34.3%) required TPN support in our study. These results are somewhat different from the randomized trial by Bolwell et al that reported TPN use by 19% patients in the methotrexate free arm and TPN use by 64% patients in the methotrexate arm. The difference in results may be explained by the small sample size in that study with 21 patients and 19 patients in each arm respectively.[12] In contrast to a retrospective study by Robien et al, we did not find any correlation between body mass index (BMI) and degree of mucositis. Robien et al had used methotrexate (15mg/ m2) for GVHD prophylaxis and the correlation with mucositis was thought to be due to increasing dose of chemotherapeutic agents with increasing BMI. [25]

In this retrospective analysis, we have ascertained the severity of OM and related complications in CD34+ selected TBI-based transplants. This is the largest study addressing

OM in TBI-based CD34+ selected transplants. Patients were uniformly treated, these were all HLA-identical sibling transplants and palifermin was not used. However, the study is limited by being a retrospective chart review at a single center without a control arm. While not ideal, retrospective review does permit the identification of the peak grade of mucositis. In the WHO scale, the extent of functional limitation (ability to swallow solids (grade 2), liquids but not solids (grade 3) and neither solids nor liquids (grade 4)) are easily discernible from nutritionist charting. Also, the Bearman RRT scale allows distinctive differentiation between grade 1 (no IV pain medication) from grade 2 (IV narcotics) and grade 3 (intubation for airway protection). For instance, one of our CD34+ selected patients required intubation for airway protection. More accurate assessments of OM, particularly related to the kinetics and duration, certainly require regular prospective monitoring by trained observers. Prospective monitoring also offers the opportunity to examine not only the peak but also the duration of OM, exemplified by the Clinical Trials Network (CTN) study reported by Cutler, et al.[13]

Genetic and metabolic determinants of the risk of mucositis after intense chemo-radiation are being discovered and could help stratify patient risk. Most polymorphisms identified so far focus on the folate/methotrexate pathway [26–28,11] but the cytochrome p450 pathway[29] has also been found significantly involved in the risk of OM. Understanding the impact of polymorphisms could not only impact risk stratification but also treatment strategies.[30] We did not test for genetic polymorphisms in our cohort of patients.

In conclusion, this study has shown that CD34+ selection in the setting of a TBI-conditioned allogeneic transplant is associated with tolerable rates of oropharyngeal mucositis. The risk and severity of OM deserves study as an important secondary endpoint in planned randomized studies of Miltenyi CD34+ selection.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
WHO and Bearman grading for oropharyngeal mucositis scores are moderately correlated

A **B**

Figure 2.
Oropharyngeal mucositis severity based upon conditioning intensity

A **B** **C**

Figure 3.
Oropharyngeal mucositis and total parenteral nutrition, narcotic and hospital length of stay

Table 1

Baseline characteristics of the subjects

	Fully ablative/Age<55 years n (%)	Reduced intensity/Age >55 years n (%)	p-value
Number of patients	82 (78%)	23 (22%)	
Gender			1
Male	41 (50%)	12 (52%)	
Female	41 (50%)	11 (48%)	
Ethnicity			0.03
Hispanic/Latino	50 (61%)	8 (35%)	
Non-Hispanic	32 (39%)	15 (65%)	
Body mass index			1
> 25	55 (67%)	15 (65%)	
25	27 (33%)	8 (35%)	
Diagnosis			0.03
ALL	25 (30%)	4 (17%)	
AML	35 (43%)	9 (39%)	
MDS	11 (13%)	6 (26%)	
CLL/NHL/B cell lymphoma	2 (2.4%)	3 (13%)	
CML/other leukemia's	9 (11%)	1 (4%)	
Disease Status at transplant			1
ALL			
CR1	19 (23%)	3 (13%)	
CR2	5 (6%)	1 (4%)	
AML			0.26
CR1	14 (17%)	5 (22%)	
CR2	17 (21%)	2 (9%)	
Active disease	3 (4%)	2 (9%)	
CMV Status (Donor -Recipient)			0.78
Positive – Positive	51 (62%)	12 (52%)	
Negative – Negative	12 (15%)	5 (22%)	
Negative – Positive	11 (13%)	3 (13%)	
Positive – Negative	8 (10%)	3 (13%)	
ECOG			0.03
0	72 (88%)	16 (70%)	
1 to 2	10 (12%)	7 (30%)	

ALL, acute lymphoid leukemia; AML, acute myelogenous leukemia; CML, chronic myeloid leukemia; CLL, chronic lymphoid leukemia; MDS, myelodysplastic syndrome; NHL, non-hodgkins lymphoma; CMV, cytomegalo virus.

Table 2

Post transplant outcomes

	Fully ablative/Age<55 years n (%)	Reduced intensity/Age >55 years n (%)	p-value
OM WHO grade 0–2	47 (57%)	22 (96%)	0.0006
OM WHO grade 3–4	35 (43%)	1 (4%)	
Stomatitis: Bearman Toxicity Scale			<0.001
Grade 0	17 (21%)	16 (70%)	
Grade 1	49 (60%)	7 (30%)	
Grade 2	16 (19%)	0 (0%)	
Mean days to ANC >500 (CI)	13.5 (12.7–14.2)	11.9 (10.9–12.8)	0.02
Bacteremia	52 (63%)	19 (83%)	0.12
Febrile Neutropenia	77 (94%)	20 (87%)	0.36
aGVHD			0.14
Grade 0–1	40 (49%)	15 (65%)	
Grade 2–4	42 (51%)	8 (35%)	
TPN (days) Mean (CI)	3.84 (2.58–5.11)	1.3 (–0.41–3.20)	0.02
IV Narcotics Mean (CI)	0.9 (0.44–1.52)	0.3 (–0.37–1.06)	0.15
LOS Mean (CI)	33.2 (29.6–36.9)	34.9 (29.2–40.6)	0.12

OM, oral mucositis; ANC, absolute neutrophil count; TPN, total parenteral nutrition; LOS, length of stay in the hospital.