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Patient reports of complications of bone marrow transplantation

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Abstract In recent years, significant improvements have been made in the management of neutropenia and thrombocytopenia and other potentially life-threatening complications of ablative chemotherapy. While these complications are of particular concern to physicians, patients receiving ablative therapy for bone marrow or blood stem cell transplants are often troubled by other side effects such as nausea, vomiting, diarrhea and mouth sores. The purpose of the study was to gain a better understanding of patients' experiences while undergoing a transplant. The same professional medical interviewer conducted in-depth interviews with 38 subjects (10 men, 28 women; mean age 46.9 years) who had received ablative therapy for bone marrow and/or peripheral blood stem cell transplants. Participants were consecutively identified through physician and patient referrals, cancer and BMT patient support groups, and newspaper advertisements. Twenty-eight patients (74%) received autologous stem cell transplants and 10 patients (26%) received allogeneic transplants. Participants reported mouth sores, nausea and vomiting, diarrhea, and fatigue as the most troubling side effects of their transplants. Mouth sores were selected as the single most debilitating side effect (42%), followed by nausea and vomiting (13%). Many patients mentioned that mouth sores made it difficult or impossible to eat ($n=23$), swallow ($n=21$), drink ($n=17$), and/or talk ($n=8$). Twenty patients reported pain in the mouth, throat, and/or esophagus. Two-thirds (66%) of patients reported receiving opioid analgesics, most frequently morphine, to relieve oral pain. For many, opioids caused incapacitating side effects, including hallucinations, a feeling of loss of control and a decrease in mental acuity. Patients receiving ablative chemotherapy identify oral mucositis as a significant cause of suffering and morbidity. Effective interventions to alleviate this complication are urgently needed.

Key words Marrow transplantation · Complications · Oral mucositis

Introduction

In recent years, significant improvements have been made in the management of neutropenia and thrombocytopenia and other potentially life-threatening complications of ablative chemotherapy. While these complications are of particular concern to physicians, patients receiving ablative therapy for bone marrow or blood stem cell transplants are often troubled by other side effects, such as nausea, vomiting, diarrhea and mouth

sores. Fortunately, with the increased availability of effective anti-emetic agents, the incidence of acute nausea and vomiting has decreased substantially [12, 15, 17]. Oral mucositis, however, remains a frequent and serious complication of bone marrow transplantation and causes significant morbidity and suffering for patients. Ulcerative oral mucositis occurs in approximately 75% of patients receiving myeloablative therapy associated with bone marrow transplants [1–3, 5–7, 9, 11, 14, 16, 20–22]. To date, no therapy has been shown to effectively prevent or ameliorate oral mucositis induced by chemotherapy or radiation therapy [13].

We undertook this study to evaluate, from the patient's point of view, the impact of complications resulting from ablative therapy in preparation for blood or marrow transplant. A primary objective of the research was to develop an understanding of patients' experiences while undergoing a transplant.

Table 1 Diagnoses (*AML* acute myelogenous leukemia, *ALL* acute lymphocytic leukemia, *APML* acute promyelocytic leukemia, *CML* chronic myelogenous leukemia, *MDS* myelodysplastic syndrome)

Diagnoses	No. of patients (subtotals)	Total no. of patients (%)
Solid tumors		19 (50)
Breast cancer	16	
Ovarian cancer	3	
Acute leukemia		6 (16)
AML	3	
ALL	2	
APML	1	
Chronic leukemia		4 (11)
CML	4	
Lymphoma		5 (13)
Non-Hodgkin	3	
Hodgkin	2	
Other		4 (11)
Multiple myeloma	3	
MDS	1	
Total		38 (100)

Patients and methods

Patients

In-depth personal interviews were conducted with 38 patients who received ablative therapy for bone marrow and/or peripheral blood stem cell transplants. To be eligible for the study, patients must have (1) undergone a bone marrow or peripheral blood stem cell transplant for the treatment of malignancies, and (2) received a transplant conditioning regimen within 18 months of the scheduled interview. No attempt was made to recruit patients who had experienced oral mucositis. The original goal was to enroll 20–25 patients. Patients were consecutively identified, screened, qualified and entered into the study. Additional patients were enrolled, irrespective of when they received their conditioning regimens, due to a high level of interest in participating. Ten (26%) of the study participants were men and 28 (74%) women, ranging in age from 20 to 64 years, with a mean age of 46.9 years. Twenty-eight patients (74%) had received an autologous stem cell transplant and 10 patients (26%) had received an allogeneic transplant. Most patients (60%) had received the transplant during 1997 or 1998, nearly one-quarter (24%) had received the transplant during 1996, while the remaining 16% of patients had received the transplant between 1992 and 1995. The diagnoses are summarized in Table 1.

Methods

From May to June 1998, one individual conducted face-to-face, in-depth interviews with 38 bone marrow transplant recipients. This individual was the principal of an independent research firm. To ensure that information was collected in a standardized fashion, questions were uniformly read from one interview to another, using an interview guide (Appendix A). Probes were used to gain further insight, following unaided recall. Prior to fielding, the interview guide was piloted to ensure utility and comprehensibility. All interviews, including pilot interviews, took place in marketing research facilities located in five major metropolitan areas in the United States. Participants were identified through a variety of sources, such as physician and patient referrals, cancer and bone marrow transplant patient support groups, and newspaper advertisements. Some patients brought diaries or journals to the interview to aid recall. To facilitate data analysis and interpretation, interviews were audio recorded and video taped. Participants were compensated with honoraria for their time.

Study design

Each patient answered a series of open- and closed-ended questions about his/her transplant. To develop an understanding of the transplant experience, each patient was asked to describe the most debilitating side effects of ablative therapy from his or her perspective. After describing the most debilitating side effects, the patient was asked to select the single most debilitating side effect. Additionally, each patient was queried about changes in the condition of the mouth and throat, including alterations in taste. If a patient had experienced changes in the oropharynx, further questions were posed to elucidate what types of alterations had occurred and whether any of these changes had had an impact on health, treatment, or overall wellbeing. Information was also gathered about hospitalization and outpatient care, and time to resumption of normal activities.

Results

Most patients received their transplant at an academic medical center (Table 2). Of the 28 patients who received autologous transplants, only 3% were hospitalized from stem cell collection through reinfusion. In contrast, 55% of patients who received allogeneic transplants were hospitalized from the time they received the conditioning regimen through the bone marrow/stem cell infusion. The average reported length of hospitalization for all patients was 28 days (range 10–60 days).

Table 2 Institutions

Metropolitan area	Institution	No. of patients (%)
Dallas	Baylor University Medical Center	6 (16)
Greater Los Angeles	Cedars-Sinai Medical Center; City of Hope; University of California at Los Angeles; University of Southern California	9 (24)
Greater Philadelphia	Abington Hospital; Allegheny-Graduate University Hospital; Cooper Medical Center; Temple University Hospital; Thomas Jefferson University Hospital; University of Pennsylvania	10 (26)
San Francisco Bay area	Alta Bates Hospital; Stanford Hospital; University of California at San Francisco	5 (13)
Seattle	Fred Hutchinson Cancer Center; Swedish Hospital; Virginia Mason Hospital	8 (21)

Nearly all (90%) of the study participants reported a change in sense of taste during the transplant. Changes included complete loss of taste (34% of patients) and altered taste (56% of patients). Over one-fifth (21%) of patients spontaneously commented that solids and liquids tasted "awful" or "horrible." Over three-quarters (79%) of the patients reported oropharyngeal changes during their treatment. Of those receiving allogeneic transplants, all (100%) experienced changes, while 71% of those receiving autologous transplants reported changes. Oral pain, sores, tender/sensitive mouth, and the development of thick mucus were the symptoms most frequently mentioned. Palliative therapies mentioned by participants included saline rinse, Peridex (chlorhexidine), nystatin, and a variety of institutionally prepared mouthwashes. Without prompting, two-thirds (66%) of patients reported receiving opioid analgesics, most frequently morphine, to treat the oral pain. Many patients reported experiencing incapacitating side effects of morphine including hallucinations, a feeling of loss of control, and a decrease in mental acuity. For some, the side effects were so significant that they chose to discontinue opioid analgesic use. Additionally, over one-half (53%) of patients reported receiving total parenteral nutrition (TPN).

Participants reported mouth sores, nausea and vomiting, diarrhea, and fatigue as the most troubling side effects. Mouth sores were selected as the single most debilitating side effect (Fig. 1) by 42% of the patients, followed by nausea and vomiting (13%). For many patients, mouth sores made it difficult or impossible to eat

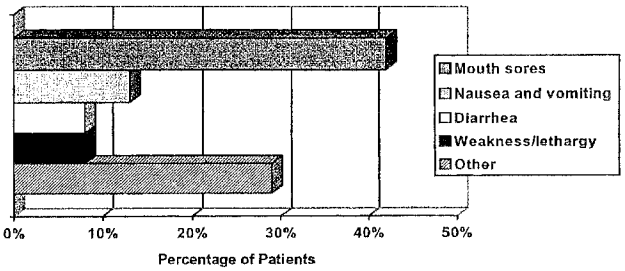

Fig. 1 The single most debilitating side effect for bone marrow transplant patients

($n=23$), swallow ($n=21$), drink ($n=17$), and/or talk ($n=8$). Twenty patients reported pain in the mouth, throat, and/or esophagus. Some patients reported excess mucus, gagging, sleep disturbances, and drooling as other complications of mucositis.

Discussion

Oral mucositis was the complication cited as the single most debilitating toxicity of ablative chemotherapy. Pain was frequently accompanied by the inability to eat, swallow, drink and talk, which necessitated narcotic therapy and supplemental nutrition. Although this study involved a small number of patients ($n=38$), characteristics of the participant pool, including leading indications by transplant type, resemble national patient data [19], suggesting that the study participants may be representative. In addition, personal interviews, in contrast to self-administered questionnaires and telephone interviews, allow the interviewer to collect highly detailed, complex, in-depth data, which may partly offset the disadvantage of a small sample size. Such a qualitative study is customarily undertaken before a larger, more costly quantitative research study.

The results of this study underscore the impact that oral complications have on the quality of life and daily functioning of patients undergoing bone marrow or stem cell transplants. Importantly, oral complications are a major source of pain, necessitating the use of opioid analgesics and total parenteral nutrition [4, 8, 14, 20].

Although most patients received their transplant within 18 months of the interview, the retrospective design of this study has inherent limitations. It is plausible that the percentage of patients reporting use of opioid analgesics and TPN in this study may under-represent actual use. While numerous studies show that approximately 75% of patients develop symptomatic oral mucositis [1–3, 5–7, 9, 11, 14, 16, 20–22], the relative importance of this complication to patients, compared to oth-

er side effects of myeloablative therapy, may not have been fully realized. This is particularly true for patients receiving ablative therapy for an autologous transplant. Oral mucositis is reported more frequently in patients receiving ablative chemotherapy and total-body irradiation for allogeneic donor transplants [2, 4, 6, 13]. The majority of patients in this study had received ablative therapy for autologous, peripheral blood stem cell transplants.

In its most severe form, ulcerative oral mucositis may be a source of systemic infection caused by colonization with abnormal bacterial flora in association with neutropenia [5, 10, 11].

In addition, oral mucositis is associated with significant economic costs due to prolonged hospitalization and changes in therapy [2, 16]. Ruescher et al. [16] reported that patients who experienced oral mucositis while undergoing autologous transplants were hospitalized, on average, 5 days longer than those who did not experience oral mucositis. The extension of time in the hospital resulted in additional charges of $22,500 per patient. More recently, increasing recognition of the significance of this complication has led to interest in prevention and treatment of oral mucositis and attendant symptoms. Such interest should lead to better therapeutic choices, thereby improving the quality of life for patients undergoing marrow transplantation. Improved quality of life may be achieved through a reduction in the need for opioids, freeing patients from debilitating CNS side effects. In addition, effective therapy may result in reduced need for treatment with systemic antibiotics and total parenteral nutrition, thereby allowing shorter periods of hospitalization and decreased total cost of patient care.

This survey represents the first in-depth evaluation of complications of myeloablative therapy from the perspective of patients. Oral mucositis was ranked as considerably more debilitating than other complications, including nausea and vomiting, diarrhea, and fatigue. These findings warrant further studies and interventions to prevent and ameliorate the signs and symptoms associated with this single most debilitating side effect of marrow transplantation.

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Appendix A: Questionnaire for one-to-one interviews with bone marrow/stem cell transplant patients

Participant's name:

Date of interview:

Interview no.:

Introduction (3 minutes)

The purpose of this interview is to develop a better understanding of your experiences while undergoing a transplant, and to determine the acceptability of three different placebo forms of a product that are currently being developed for treatment of mouth sores that transplant patients may experience. The interview should last about 50 minutes. Do you have any questions before we begin?

Transplant experience (8 minutes)

1. What type of transplant (e.g., allogeneic, autologous, bone marrow, peripheral blood) did you receive?
2. What side effects, if any, did you experience during your transplant that were most debilitating and/or troublesome?
3. What part of your transplant, if any, did you receive on an outpatient basis?
4. How long after your transplant were you able to resume your normal activities?

5a. During your transplant was your sensation of taste altered in any way, or not?
- Yes→Go to next question
- No→Skip to question #6

5b. How was it changed?

Oral mucositis (10 minutes)

6a. Please describe the oral mouth conditions, if any, that you experienced · during or following your transplant? (Probe for: redness, tingling, swelling, burning, pain, mouth sores, etc.)

6b. When during your transplant did *(condition identified in #6a)* develop?

6c. How long did *(condition identified in #6a)* last?

6d. Which of these conditions/symptoms were most debilitating and/or troublesome to you? (Probe: How did the relative severity of the mucositis compare to the other side effects that you experienced?)

7. What medical care did you receive, if any, when these conditions developed? (Probe for TPN, narcotic analgesics, swishes, etc.)
8. What effect(s), if any, did these oral conditions have on your overall health and/or treatment experience? (Probe for inability to eat, drink, sleep; prolonged hospitalization; admission/readmission to hospital)
9. Did you experience any of the conditions like *(mention conditions identified in #6a)* in your throat and/or esophagus, or not?
- Yes→Which conditions?
- No

Reactions to new product and evaluation of three formulations (17–20 minutes)

Description of new product

The new product that we will be discussing is currently being tested as a prevention and/or treatment of mouth sores associated with a marrow or blood stem cell transplant for the treatment of cancer. It is an oral formulation that is self-administered by the patient into his/her mouth. The patient is instructed to retain the product in his/her mouth for a few minutes, 6 times a day. Patients begin taking the product 4 days prior to their bone marrow or peripheral blood stem cell transplant, before the potential onset of symptoms, and continue taking it for a period of up to 21 days. The product is currently being evaluated in patients who are undergoing a transplant in the hospital.

Order of presentation of the placebo formulations will be rotated from one interview to another. Formulations will be labeled Placebo #10, Placebo #20, and Placebo #30. Participant will be asked to retain the first placebo formulation in his/her mouth for a total of 5 minutes; the remaining two formulations will be retained for approximately 3 minutes each.)

Instructions to patient

To assess the acceptability of the placebo formulations we would like for you to test each one. Before testing, please rinse your mouth with water. Then dispense the placebo into your mouth, and hold it for approximately 5 minutes. Feel free to administer the placebo as slowly as you prefer within the 5-minute time period. Please move the placebo around in your mouth using your tongue to evenly coat the oral cavity. After 5 minutes, feel free to empty the contents of your mouth into a paper cup.

Placebo #10

10.a. On a scale from 1 to 5, where 1 is not at all acceptable and 5 is completely acceptable, how would you rate the overall acceptability of this oral product?
10b. Why do you rate the acceptability at this level?
10c. What features of this product, if any, do you like?
10d. What features of this product, if any, do dislike?
10e. What percentage of your mouth would you estimate was covered by this oral product?

Placebo #20

11a. On a scale from 1 to 5, where 1 is not at all acceptable and 5 is completely acceptable, how would you rate the overall acceptability of this oral product?
11b. Why do you rate the acceptability at this level?
11c. What features of this product, if any, do you like?
11d. What features of this product, if any, do dislike?
11e. What percentage of your mouth would you estimate was covered by this oral product?

Placebo #30

12a. On a scale from 1 to 5, where 1 is not at all acceptable and 5 is completely acceptable, how would you rate the overall acceptability of this oral product?
12b. Why do you rate the acceptability at this level?
12c. What features of this product, if any, do you like?
12d. What features of this product, if any, do dislike?
12e. What percentage of your mouth would you estimate was covered by this oral product?
13a. Of the three formulations that you tested, which one is *most acceptable* from your perspective?
- Placebo #10
- Placebo #20
- Placebo #30

13b. Why did you select Placebo # ?
14a. On a scale of 1 to 5, where 1 is not at all willing and 5 is fully willing, how willing would you have been to use (*mention most acceptable option*) during your transplant as a prevention and/or treatment of mouth sores?
14b. Why do you rate your willingness at that level?
15a. Of the three formulations that you tested, which one is *least acceptable* from your perspective?
- Placebo #10
- Placebo #20
- Placebo #30

15b. Why did you select Placebo # ?
16a. On a scale of 1 to 5, where 1 is not at all willing and 5 is fully willing, how willing would you have been to use (*mention least acceptable option*) during your transplant as a prevention and/or · treatment of mouth sores?
16b. Why do you rate your willingness at that level?

Questions relating to all three forms

17. On a scale of 1 to 5, where 1 is not at all acceptable and 5 is completely acceptable, how acceptable

to you was the 5-minute time period that you were required to hold the product in your mouth?

18. What is the maximum number of times per day you would have been willing to use:
    - *(mention placebo selected as most acceptable option)* during your transplant
    - *(mention placebo selected as least acceptable option)* during your transplant
19. If the directions for use recommend swallowing the product after holding it in your mouth for a specified time period, would you:
    - have been willing to do so during your transplant? Why or why not? (Probe for difference between most and least preferred forms.)
    - have been able to do so during your transplant? Why or why not? (Probe for difference between most and least preferred forms.)
20. On a scale of 1 to 5, where 1 is not at all acceptable and 5 is very acceptable, how acceptable to you was the temperature of these placebo formulations when they were first placed in your mouth?
21. On a scale of 1 to 5, where 1 is not at all acceptable and 5 is very acceptable, how acceptable to you was the taste of these placebo formulations?
22. What additional suggestions, if any, do you have regarding ways in which any one of these three formulations may be improved?

Alternative formulations (7–9 minutes)

23. There are six alternative dosage forms being considered for this new product for which we would like your feedback. I will lay these out on the table, name/describe each one, and place a descriptor card in front of each alternative. Please consider each one, and then place the cards in order to reflect your preferences. The card placed on the top of the stack should represent the dosage form that you most prefer; the one on the bottom is the dosage form that you least prefer. (*After respondent ranks the products, record their rankings in the following table.*)

Dosage form	Rank
Glycerin drop	
Spray	
Lozenge	
Slow-release tablets	
Gum	
Film coating	

23a. Why did you rank (*mention alternative ranked as number #1)* as the alternative that you most prefer?

23b. Why did you rank (*mention alternative ranked as number #6)* as the alternative that you least prefer?

24a. Now, please consider which one of the following two alternatives you most prefer:
    - (*#1 choice of current formulation*), *versus*
    - (*#1 choice of alternative dosage form*)?

24b. Why did you make this choice?

25. That was my last question. Do you any additional comments or suggestions for the company that is developing this new product?

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