# The Gulf Journal of Oncology

Indexed By PubMed and Medline Database

Issue 10, July 2011
ISSN No. 2078-2101


The Official Journal of the Gulf Federation For Cancer Control

# The Gulf Journal of Oncology

**ISSUE 10** **JULY, 2011**

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# Early Gastrointestinal Complications of Stem Cell Transplant - Results of Prospective Study at IRCH, AIIMS, India

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## Abstract

### *Background*

The study was conducted with the purpose of finding clinical profile of early gastrointestinal complications of stem cell transplant at this center.

### *Methods*

70 consecutive subjects, who were subject to bone marrow transplant from October 2002 to September 2004, were prospectively studied. The gastrointestinal complications were followed in first 100 days of transplant and recorded in a pre-determined format.

### *Results*

Study population comprised of 23 allo-transplant (with 3-non-myelablative procedures) and 47 auto-transplant subjects. Gastrointestinal complications included: nausea and vomiting occured in 19 (82.60%), mucositis- 20 (86.95%), diarrhea- 15 (65.21%), veno-occlusive disease (VOD) - 3 (13.04%) and acute pancreatitis- 1 (4.34%) in allo-transplant group. Nausea and vomiting occurred 36 (76.59%), mucositis- 46 (97.88%) diarrhea- 39 (82.98%), VOD- 5 (10.64%) in auto- transplant subjects. Acute graft versus host disease (AGVHD) involved gut in 3 and liver in 1 case of allo-BMT-group.

### *Keywords*

*Stem cell transplant, Mucositis, Veno-occlusive disease, Graft versus host disease.*

## Introduction

Gastrointestinal complications are an important cause of morbidity and even deaths in the early post bone marrow transplant period. To determine the incidence of various gastrointestinal complications and their impact on the course and outcome of transplant, a prospective study was conducted at this north Indian facility. Such studies inculcate understanding and training in the field of oncology. There are a few bone marrow transplant centers in India. In a south Indian center, allogenic transplant procedures are done whereas at IRCH, AIIMS, both autologous and allogenic transplants are carried out. In addition bone marrow transplants are carried out at TMH Mumbai but in none of these centers any prospective study of early gastrointestinal BMT complications has been conducted[1-4]. This study thus represents first of its kind in the country.

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## Material and methods:

A total of 70 consecutive patients were enrolled from September 2002 to October 2004 and their pre-transplant status were evaluated and recorded. Study population comprised of 23 allo-transplant (with 3-non-myelablative procedures) and 47 auto-transplant subjects. There were 18 males and 5 females with age ranged from 4-42 years (median-23) in allo-transplant group. They included CML.-CP- 9, CML.-AC-2, CML.-BC-2, AML-4, aplastic anemia-3, Hurlers syndrome-2, thalassemia major-1. The auto-transplant patients included 25 males and 12 females, age ranged from 4 to 68 years (median-47). Their diagnosis was - MM-29, HD-8, NHL-6, AML-3, neuroblastoma-1. BuCy (busulphan+cyclophosphamide) and high dose melphalan were the main preparatory regimens. Hospital course of each patient from the day of preparation to the time of discharge was carefully assessed, followed and recorded in the protocol. Clinical and relevant laboratory

parameters were studied. Events like harvesting bone marrow or peripheral blood stem cells, conditioning, harvest infusion, pre-engraftment time, engraftment process and post-engraftment period and early gastrointestinal along with other complications were followed, assessed and recorded. Early bone marrow transplant (BMT) complications were defined as those occurring in first 100 days of the procedure. Complications were graded as per National Institute of Health (NIH), Common Toxicity Criteria version 3 or standard grading systems, wherever applicable. Neutrophil and platelet engraftment were defined as first day of three consecutive days of achieving absolute neutrophil count (ANC) and unsupported platelet count of 500/mm3 and 20,000/mm3 respectively. Final analysis was carried out using appropriate statistical methods.

## Results:

A total of 70 cases were included in the study. This number comprised of 47 cases for auto-transplant with median age of 68 years (range-9-68) and 23 subjects for allo-transplant with median age of 23 years (range-4-22). Out of 23 allo-BMT subjects 20 underwent myloablative

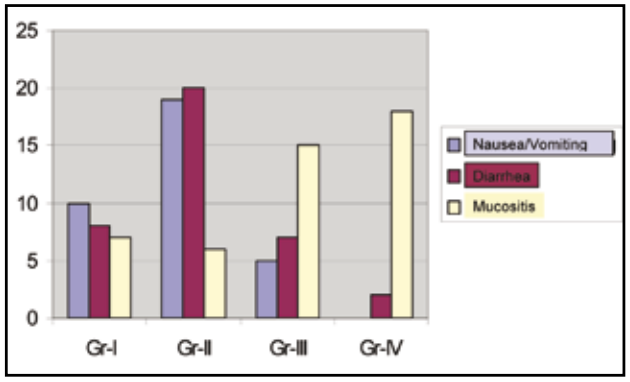


**Fig. 1(a): Comparison of Grades of Nausea/Vomiting, Diarrhea, Mucositis**

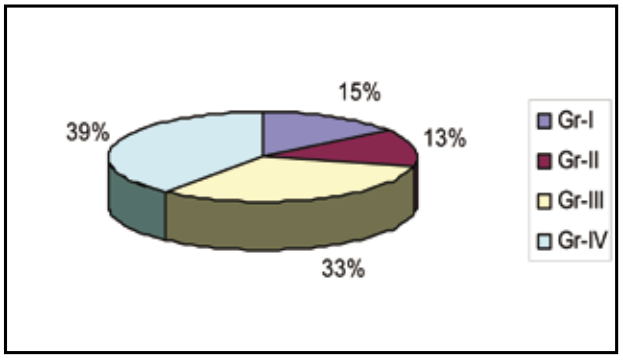


**Fig. 1(b): Grades of Mucositis-Overall**

| Complications | Auto-BMT- No (%) | Allow-BMT No (%) |
|---|---|---|
| Nausea & Vomiting | 36 (76.59) | 19(82.60) |
| Mucositis | 46(97.88) | 20(86.95) |
| Diarrhea | 39 (82. 98) | 15(65.21) |
| VOD | 5 (10.64) | 3 (13.04) |
| Acute Pancreatitis | | 1 (4.34) |

**Table 1 : Early Gastrointestinal Complications (days 0-30) in Auto- and Allo-BMT Patients**

| Complication | Auto-BMT No (%) | Allo-BMT No (%) |
|---|---|---|
| Hyperacidity, Erosive gastritis | 1 (2.85) | |
| Malena | 1 (2.85) | |
| Anorectal bleed, tenesmus | 1 (2.85) | |
| Nausea, Vomiting, Dysgeusia, Anorexia | Common | Common |
| Abdominal pain | Occasional | |

**Table 2 : Early interim (30-100 days) Gastrointestinal Complications: Auto- & Allo-BMT**

| | Auto-BMT | Allo-BMT |
|---|---|---|
| No | 5 | 2 |
| Incidence (%) | 5/35 (14.3) | (2/16) 12.5 |
| Onset-median (range) | 9 (5-22) | 13.5 (6-21) |
| Grade | | |
| I | 1 | 1 |
| II | 3 | 1 |
| III | 1 | 0 |
| Outcome | | |
| I | Recovered | Died (EF) |
| II | 2 Recovered; 1 Died (MOF) | Died (MOF) |
| III | Recovered | - |

**Table 3 : Hepatic Veno-occlusive Disease (VOD) (Bearman)**

treatment and the remaining 3 received non-myeloablative treatment. Majority of auto-SCT patients (61.70%) received high dose melphalan as conditioning, followed by CBV regimen (25.53%). Most of allo-BMT patients (82.60%) received BUCY as the preparatory regimen. In the early post transplant period, mucositis was almost universal in auto-transplant patients but was slightly less incident in allo-transplant group. Nausea, vomiting and diarrhea were also very common (Table 1a & 1b). Most of the patients (72 %) showed grade III and IV mucositis where as less than one third (28 %) suffered from grade I and II mucositis (Fig. la and 1b). Mucositis lasted for a mean and median duration of 10 and 11 days (range-1-20) in Auto-Transplant Group and 10.7 and 10.6 days (range-4-24) in Allo-Transplant Group respectively (data not shown). Common problems that occur after one month of auto-stem cell or bone marrow transplant (SCT/

BMT) are akin to convalescence period. Some of the manifestation is related to gastrointestinal tract (Table 2). Pattern of venooclusive disease and gut acute versus host disease (AGVHD) is shown in Tables 3 and 4 respectively. Clinically, lungs constituted the major source of infection in 20 (28.57%) followed by gastrointestinal tract in 15 (21.43%) and central line site in 5 (7.14%) cases (Table 5).

| Grade | No | Grade I | Grade II | Grade III | Grade |
|---|---|---|---|---|---|
| Site | | | | | |
| Skin | 7 | 4 | 2 | 0 | 1 |
| Liver | 1 | | | | 1 |
| Gut | 3 | | | 2 | 1 |
| Outcome | Recovered | Recovered | Recovered | Recovered | Died of ARF |

**Table 4 : AGVHD involving Liver and Gut (Allo-BMT)**

| Clinical Sites | 100% | Percentage |
|---|---|---|
| Lung | 15 | 29.41 |
| Pneumonitis | 10 | |
| Tuberculosis | 3 | |
| Fungal | 2 | |
| Sinusitis | 2 | 3.92 |
| Fungal | 1 | |
| Gut | 13 | 25.49 |
| Syphilitic | 6 | |
| Perineal | 7 | |
| Catheter | 4 | 7.84 |
| Herpes Zoster | 1 | 1.96 |

**Table 5 : Source of Infectious Complications**

## Discussion:

In this cohort of SCT/BMT (stem cell transplant/ bone marrow transplant) patients, majority, i.e., about 2/3 of the patients underwent autologous transplantation, this center catering mainly to oncological problems. Whereas in a Southern Indian BMT center, basically a hematological unit, there is a larger experience with allogeneic transplant[2]. Pattern and incidence of early post-bone marrow transplant complications in this cohort of patients simulate that reported in other Indian and western literature with some exceptions. Most of our auto-transplants were conducted on patients suffering from multiple myeloma as in other transplant centers and received high dose melphalan as preparatory regimen. Symptoms of nausea and vomiting occurred in more than three-fourths of our patients (76.59% and 82.60% of auto- and allo- groups respectively) despite regular round the clock anti-emetics. Dix and colleagues evaluated the role of a continuous infusion, patient-controlled anti-emetic pump in patients undergoing autologous bone marrow transplant. During high-dose chemotherapy, patients received a serotonin antagonist plus dexamethasone followed by a combination of diphenhydramine, lorazepam, and dexamethasone given via continuous infusion; they also were able to receive rescue bolus doses, via PCA (patient-controlled anti-emetic) pump for breakthrough nausea and vomiting. Patients remained on the pump for a median of nine days. Control of emesis or complete overall control of emesis (no emesis or nausea) was achieved in 75% of patients during the time they were receiving chemotherapy and 35% of patients after chemotherapy[5]. Thus control of nausea and vomiting in the BMT setting continues to be suboptimal, with complete control rates ranging from 50%-75% with an adverse effect on quality of life (QOL) and early morbidity since these symptoms are invariably associated with anorexia and low intake[5, 6]. Thus anorexia, nausea, recurrent vomiting and exhaustion plague the early course after SCT/ BMT. Symptomatic relief of anorexia, nausea, vomiting, diarrhea, and exhaustion warrant more measures and strategies to evaluate and relieve them. Recent American Society of Clinical Oncology (ASCO) guidelines advocate a three drug combination of a 5-Hydroxytryptamine-3 (5-HT3) serotonin antogonist, dexamethasone and aprepitant, a neurokinin receptor-l antagonist for optimal results before chemotherapy of high emetic risk[7]. Nearly all (97.88%) in auto-BMT and about 86.95% in allo-BMT series of our patients suffered from mucositis and vast majority had grades III and IV mucositis. Overall 72% suffered from Gr. III and IV mucositis. Mucositis lasted for a median duration of 11 days (range-1-20) and 10.6 days (range-4-24) in auto- and allogeneic groups respectively. Occurrence of mucositis is universal, with majority of patients suffering from Grade III and IV mucositis with

accompanying agony. Incidence is consistent with that reported in literature[8]. Mucositis pain amelioration is better with pain relieving methods such as patient controlled analgesia (PCA) to improve short-term QOL post-transplant procedure needs emphasis. Paliferin has been found to be effective in preventing its manifestations[9]. More than four-fifth cases (82.98% in auto-BMT) and about two-third cases (65.21% in allo-BMT) had diarrhea of various grades. The occurrence of veno-occlusive disease was similar in auto- and allo-BMT groups, viz 10.64% and 13.04% respectively. The median day of onset was 9 (range 5-21) and 13.5 (range-6-21) days in the auto-BMT and allo-BMT respectively. VOD was of Bearman grade I (n-1), II (n-1), III (n-1) in allo-group and I (n-1), II (n-2), III (n-1) in auto-group. 3 out of 5 cases in auto-BMT and none of the cases in allo-BMT cases survived. All deaths occurred due to multi-organ failure. However, as the number of patients in allo-group is small, it may not reflect the true incidence of veno-occlusive disease (VOD) of liver. Clinically manifest veno-occlusive disease has been reported to occur in 36% of allo-transplant patients conditioned with busulphan containing regimen with about one-fourth of them being life threatening[10-13]. There are reports that 10-60% patients develop this complication with 70% cases recovering spontaneously or with difibrotide treatment[14]. Incidence in this series is towards lower limit of reported one. VOD occurred in 2/11 (18.18%) cases of advanced CML (AP and BC) cases in an earlier retrospective analysis of a small patient cohort at the same center but none in CML-CP cases[1, 3]. One case of CML-BC with grade IV acute graft versus host disease (AGVHD). This patient developed liver and gut involvement with grade IV diarrhea and finally succumbed to multiorgan failure. One of the allogenic subjects developed acute pancreatitis. Relation of various gastrointestinal complications with age, sex and previous chemotherapy exposure was not ascertained in this study. Clinically gastrointestinal constituted the second major source of infection in 15 (21.43%) cases with perineal sepsis and neutropenic colitis as the commonest manifestations. Gastrointestinal tract was the source of sepsis in 15 (21.43%) with 7 cases of enterocolitis, 8 of parianal sepsis and 1 of clostridium difficili. Perenial sepsis is a common event in early post-BMT period[15-17].

## Conclusion:

Early gastrointestinal complications include nausea and vomiting, mucositis, and diarrhea in majority of this patient cohort. Veno-occlusive disease (VOD) occurred in approximately one in ten patients. Some suffered from acute graft versus host disease. One of the patients developed an acute pancreatitis. Further, gastrointestinal tract was an important source of infection.

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