Original Article

Opioid Administration for Mucositis-Related-Pain Using Patient Controlled Analgesia (PCA) Method is Associated with the Development of Early Posttransplant Complications

Mukozit İlişkili Ağrı için Hasta Kontrollü Analjezi Yöntemi Eşliğinde Uygulanan Opioid Tedavisinin Erken Dönem Nakil Komplikasyonları ile İlişkisi

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ABSTRACT

Introduction: Mucositis is one of the major complications of allogeneic hematopoietic stem cell transplantation with myeloablative conditioning. Several measures have been developed to improve pain palliation and quality of life in transplant recipients. This study was performed to evaluate the association of opioid administration using patient controlled analgesia (PCA) method with early posttranplant complications.

Materials and Methods: Medical records of 452 patients [median age: 35(15-67) years, male/female: 285/167] were retrospectively reviewed.

Results: PCA was used in 157 patients (34.7%) for median 9(1-24) days. The proportion of patients who received myeloablative conditioning regimen was significantly higher in PCA+ group ($p<0.001$). Severe mucositis was more common in patients who required PCA administration ($p<0.001$). Total body irradiation ($p<0.001$) and methotreaxate prophylaxis ($p<0.001$) were more frequently used in PCA+ patients. Hypoxia, bleeding, sinusoidal obstruction syndrome, invasive fungal infections, neurotoxicity, hepatotoxicity and nephrotoxicity were significantly more common in PCA+ patients. Duration of hospitalization was significantly longer in PCA+ group ($p<0.001$).

Discussion: Opioid administration with PCA, which was more frequently used in patients who had myeloablative conditioning and mucositis, was found to be associated with the development of early posttransplant complications.

Keywords: Patient Controlled Analgesia; Myeloablative Conditioning; Mucositis; Allogeneic Hematopoietic Stem Cell Transplantation; Pain Palliation

ÖZET

Giriş: Mukozit, myeloablatif hazırlama rejimiyle allojeneik kök hücre nakli yapılan hastalarda gelişebilen önemli komplikasyonlardan biridir. Kök hücre nakil alıcılarında ağrı palyasyonu sağlamak ve yaşam kalitesini artırmak için farklı yöntemler geliştirilmiştir. Bu çalışmanın amacı, hasta kontrollü analjezi (HKA) yöntemi eşliğinde uygulanan opioid tedavisinin erken dönem nakil komplikasyonlarıyla ilişkisini araştırmaktır.

Gereç ve yöntemler: Toplam 452 hastanın [ortanca yaş: 35(15-67) yıl, erkek/kadın: 285/167] verileri geriye dönük olarak incelendi.

Bulgular: Hasta kontrollü analjezi 157 hastada (%34.7) ortanca 9(1-24) gün süreyle uygulandı. HKA+ grupta myeloablatif rejim uygulanan hasta sayısı anlamlı yüksekti ($p<0.001$). HKA gereksinimi olan hastalarda ağır mukozit gelişiminin daha sık olduğu gözlendi ($p<0.001$). Tüm beden ışınlaması ($p<0.001$) ve metotreksat kullanımı ($p<0.001$) HKA+ grupta daha sıktı. Hipoksi, kanama, sinuzoidal obstrüksiyon sendromu, invaziv fungal enfeksiyonlar, nörotoksisite, hepatotoksisite ve nefrotoksisite

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HKA+ grupta daha sık görüldü. Hastanede kalış süresi HKA+ grupta anlamlı uzun saptandı (p<0.001). **Tartışma:** Bu çalışmada, myeloablatif hazırlama rejimi uygulanan ve ağır mukozit gelişen hastalarda daha sık kullanılan HKA eşliğinde opioid uygulamasının erken dönem nakil komplikasyonlarıyla ilişkili olduğu gösterildi.

Anahtar kelimeler: Hasta Kontrollü Analjezi; Myeloablatif Hazırlama Rejimi; Mukozit; Allojeneik Kök Hücre Nakli; Ağrı Palyasyonu

Introduction

Allogeneic hematopoietic stem cell transplantation (alloHCT) is considered as a curative modality in the treatment of various hematological disorders. Despite favorable improvement in patient care and supportive measures, unacceptable morbidity and mortality rates remain a major problem in high risk patients. Although chronic graft versus host disease (GvHD) and relapse seem to be responsible for the long-term adverse outcomes, early posttransplant complications including mucositis, infection, acute GvHD and sinusoidal obstruction syndrome (SOS) may cause significant toxicity which may result in prolonged hospitalization and impaired quality of life [1-3].

Among a variety of transplant related factors which may increase the risk of periengraftment complications, the prominent role of conditioning regimen intensity should be pronounced in the development of severe mucositis and other complications due to endothelial dysfunction. Myeloablative conditioning (MAC) which contains high dose chemotherapy and/or radiotherapy has an adverse impact on rapidly dividing cells and may cause severe mucositis in the early posttransplant course. Approximately 75% of alloHCT recipients develop oral mucositis in the preengraftment phase of transplantation. The severity of mucositis is associated with the intensity of conditioning regimen as well as immunosuppressive medications which are used for GvHD prophylaxis such as methotrexate [4-7]. Oral nutrition may be impaired in these patients as a result of mucositis associated pain. Bacterial translocation and catheter related infections may develop in patients who require parenteral support because of oral nutrition impairment. Therefore, pain palliation including topical local anesthetics and systemic opioid analgesics is indispensable to maintain normal gastrointestinal function in order to accelerate the healing process of mucosal barriers and improve quality of life [7-9].

Patient controlled analgesia (PCA) is a pain relief method which enables self administration of the analgesic substance via intravenous bolus and/or infusion using a specific pump which is programmed by an expert, preferably by an anesthesiologist. Maximum drug dose, dose ranges and infusion rates can be individualized by this procedure. The total amount of opioid substance was shown to be significantly reduced in patients who receive PCA [8,10].

To our knowledge, the role of opioid administration via PCA method in the development of transplant complications has not been previously studied. Therefore, this retrospective study is performed to evaluate the effect of opioid use with PCA in the early posttransplant course and to clarify its possible association with transplant related complications and hospital stay.

Materials and Methods

Patients

A total of 452 patients [median age: 35(15-67) years, male/female:285/167] who underwent alloHCT between 2003 and 2018 were included in this study. Medical records of the patients were analyzed retrospectively. Demographic and clinical characteristics of the patients were recorded. Transplant risk assessments including European Society for Blood and Marrow Transplantation (EBMT) score and Hematopoietic Cell Transplantation Comorbidity Index (HCT-CI) were evaluated [11,12]. National Cancer Institute Common Toxicity Criteria (version 4) was used for

toxicity assessments. Patient and transplant characteristics are represented in Table 1.

Pain Management and PCA Schedule

Pain scores of the transplant recipients, which range from 0 to 10 points (pts), were determined by numeric rating scale (NRS) [9,13]. Daily pain status of all patients was questioned and recorded by transplant nurses. Tramadol infusion with PCA was started when the pain score was greater than 3 pts. Tramadol was mixed with normal saline at a concentration of 5 mg/mL. Lockout time was identified as 30 minutes while 4-hour infusion limit was indicated to be 200 mL. Initial dose arrangements were 20 mg and 5 mg/mL for bolus and infusion rates, respectively. All steps of the setting, including basal and subsequent modifications, were adjusted by an anesthesiologist. In patients with a permanent pain score greater than 5 pts, which was considered as refractory to appropriate dose increments, intravenous morphine and/or transdermal fentanyl patch were used to support PCA infusion. Antiemetic drugs such as serotonin 5-HT3 antagonists or metoclopramide were used for PCA induced nausea and vomiting. PCA infusion was stopped in case of severe side effects including dizziness, confusion and hypoxemia.

Transplant Protocols

The criteria of the Centre for International Blood and Marrow Transplant Research (CIBMTR) was used for the classification of conditioning intensity [14]. Myeloablative conditioning regimens consisted total body irradiation (TBI) (1200 cGy)/ cyclophosphamide (120 mg/kg) or busulfex (12.8 mg/kg)/cyclophosphamide (120 mg/kg), whereas fludarabine (150 mg/m^2)/melphalan (140 mg/m^2) and TBI (400 cGy)/fludarabine (150 mg/m^2) were designated as reduced intensity conditioning (RIC) regimens. Cyclosporine A / methotrexate and cyclosporine A / mycofenolate mofetil combinations were used for GvHD prophylaxis in MAC and RIC transplants respectively.

Supportive Care

Standards for antibacterial and antifungal prophylaxis, febrile neutropenia, invasive fungal infections (IFI) and cytomegalovirus reactivation were assessed based on the European Conference on Infections in Leukemia (ECIL) and Infectious Diseases Society of America (IDSA) guidelines [15-17]. The diagnosis and grading of SOS was identified according to the EBMT guidelines [18].

Statistical Analysis

Categorical and continuous variables were represented as frequency (percentage) and median (range) respectively. Kolmogorov-Smirnov and Shapiro Wilk tests were performed for normality analysis with $p>0.05$ taken as evidence of normality. Parametric and non-parametric tests were used in case of normal and abnormal distributions. Continuous variables were compared using Student T-test, Mann Whitney U and Kruskal Wallis tests. Chi-square test was used for the comparison of categorical variables. Correlation analysis was performed using Pearson and Spearman tests. Kaplan-Meier method was used for survival analysis and log rank test for the comparisons of Kaplan-Meier curves. Cox proportional hazards regression model with the calculation of HRs and 95% confidence intervals (CI) was used for univariate and multivariate analysis in order to determine statistically significant prognostic factors. IBM SPSS Statistics Version 22.0 (IBM Corp, Armonk, NY, USA) programme was used for statistical analysis. All P values were two-sided and $P<0.05$ was considered as statistically significant.

Ethical Standards

The study was approved by the institutional review board of Gazi University Faculty of Medicine (Date: 11.06.2018; Number: 449) All procedures in the study were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

Table 1. Patient and Transplant Characteristics

Age (years) [median (range)]	35 (15-67)
Gender (male/female) [n(%)]	285 (63.1) / 167 (36.9)
Diagnosis [n(%)]	
Acute myeloid leukemia	169 (37.4)
Acute lymphoblastic leukemia	109 (24.1)
Myelodysplastic syndrome	29 (6.4)
Non Hodgkin lymphoma	32 (7.1)
Hodgkin lymphoma	19 (4.2)
Multiple myeloma	25 (5.6)
Chronic lymphocytic leukemia	2 (0.4)
Chronic myeloid leukemia	14 (3.1)
Primary myelofibrosis	10 (2.2)
Aplastic anemia	34 (7.5)
Paroxysmal nocturnal hemoglobinuria	5 (1.1)
Thalassemia major	4 (0.9)
Pretransplant Disease Status (n=378) [n(%)]	
Complete remission	262 (69.3)
Partial remission	33 (8.7)
Progressive disease / Relapse	66 (17.5)
Primary refractory	15 (4)
Stable disease	2 (0.5)
ECOG Performance Status [median (range)]	1 (0-4)
HCT-CI [median (range)]	1 (0-6)
EBMT Score [median (range)]	3 (0-7)
HLA Compatibility [n(%)]	
Matched sibling	365 (80.8)
Mismatched related	14 (3.1)
Unrelated	71 (15.7)
Haploidentical	2 (0.4)
Graft Source [n(%)]	
Peripheral blood	429 (94.9)
Bone marrow	23 (5.1)
Conditioning Regimen [n(%)]	
Myeloablative	276 (61.1)
Reduced intensity	176 (38.9)
Total Body Irradiation [n(%)]	109 (24.1)
GvHD Prophylaxis [n(%)]	
Cyclosporine A–methotreaxate	379 (83.8)
Cyclosporine A–mycophenolate mofetil	73 (16.2)
Infused $CD34^+$ Cell Count ($x10^6$/kg) [median (range)]	4.2 (0.3-9.5)
Neutrophil Engrafment (days) [median (range)]	17 (7-43)
Platelet Engraftment (days) [median (range)]	15 (0-89)
Total Parenteral Nutrition [n(%)]	194 (42.9)
Duration of parenteral nutrition (days) [median (range)]	10 (2-46)
Sinusoidal Obstruction Syndrome [n(%)]	97 (21.5)
Grade [median (range)]	2 (1-3)
Thrombotic Microangiopathy [n(%)]	4 (0.9)
Duration of Febrile Neutropenia (days) [median (range)]	3 (0-52)
Septic Shock [n(%)]	35 (7.7)
Invasive Fungal Infection [n(%)]	116 (25.7)
Mechanical Ventilation [n(%)]	52 (11.5)
Pain Score [median (range)]	6 (0-10)
PCA Administration [n(%)]	157 (34.7)
Duration of PCA (days) [median (range)]	9 (1-24)
Duration of Hospitalization (days) [median (range)]	31 (9-130)

EBMT European Society for Blood and Marrow Transplantation; ECOG Eastern Cooperative Oncology Group; GvHD Graft versus Host Disease; HCT-CI Hematopoietic Cell Transplantation Comorbidity Index; PCA Patient Controlled Analgesia

Results

Median pain score was indicated to be 6(0-10) pts in the whole study population. Patient controlled analgesia was used in 157 patients (34.7%) for median 9(1-24) days. A total of 118 patients (75.2%) were diagnosed as acute leukemia in PCA+ group.

Patient controlled analgesia requirement was observed to be significantly predominant in acute leukemia patients (P<0.001). Furthermore, PCA was more commonly used in patients who received TBI (P<0.001) and cyclosporine A-methotrexate as GvHD prophylaxis (P<0.001). Patients who developed SOS (P<0.001), febrile neutropenia (P<0.001) and IFIs (P<0.001) required significantly more PCA support.

Comparison of PCA+ and PCA- Groups

Based on PCA administration, the study population was seperated into two subgroups, each of which implicates PCA+ (n=157, 34.7%) and PCA- (n=295, 65.3%) patients. Median pain score was significantly higher in PCA+ group compared to PCA- group [8(0-10) vs 4(0-10) pts; P<0.001)]. Patients in PCA+ group were found to be younger than PCA- patients [29(16-65) vs 38(15-67) years; P<0.001] which may be associated with the predominance of acute leukemia patients in PCA+ group who were frequently exposed to MAC regimens. Thus, the proportion of patients receiving MAC in PCA+ group was found to be significantly higher compared to PCA- group (79% vs 51.5%, P<0.001). Patient controlled analgesia was administered in 44.9% of the patients who received MAC regimen and 18.9% of the patients who had RIC (P<0.001). Total body irradiation (42.7% vs 14.2%; P<0.001) and methotreaxate prophylaxis (97.5% vs 76.6%; P<0.001) were observed to be more frequently used in PCA+ patients. Neutrophil [17(10-43) vs 16(7-29) days; P<0.001] and platelet engraftments [16.5(0-89) vs 14(0-64) days; P<0.001] occured later in PCA+ group compared to PCA- group. Total parenteral nutrition (TPN) was extensively used in PCA+ patients (76.4% vs 24.8%; P<0.001). Duration of febrile neutropenia was significantly longer [(5(0-52) vs 3(0-28) days; P<0.001] and IFIs were found to be more frequent in PCA+ group [38.2% vs 20%; P<0.001)]. Similarly, incidence of SOS was indicated to be higher in patients who received PCA [36.3% vs 13.6%; P<0.001]. Duration of hospitalization was recorded to be significantly longer in PCA+ patients [32(16-130) vs 29(9-94) days, P<0.001) (Table 2).

Conditioning regimen and transplant related toxicities including hypoxia (p=0.032), bleeding (P<0.001), neurotoxicity (P=0.003), hepatotoxicity (P=0.001) and nephrotoxicity (P=0.033) were observed to be more common in PCA+ patients. Table 3 represents the comparison of toxicity profiles between two groups.

Subgroup Analysis Based on Pain Status

The study cohort was further divided into two distinct subgroups based on the severity of pain, such as “mild-to-moderate” and “severe”. Maximum pain score ≥7 pts was classified as “severe” pain, whereas pain score <7 pts was referred to “mild-to-moderate” pain. Acute leukemia diagnosis (P<0.001), MAC (P=0.005) and TBI administration (P<0.001) were more frequently observed in the severe-pain group.

Survival Analysis and Prognostic Factors

Probability of overall survival (OS) was estimated to be 35.5% in the whole population at the end of 539(1-5435) days of follow-up. Probability of OS was not different between PCA+ and PCA- groups (33.2% vs 37.7%) (P>0.05) (Figure 1).

Factors which had a significant impact on OS in univariate analysis are represented in Table 4. Eastern Cooperative Oncology Group (ECOG) performance status [P<0.001; HR: 3.869 (95% CI: 1.849-8.098)], EBMT risk score [P=0.022; HR: 1.222 (95% CI: 1.029-1.451)], duration of febrile neutropenia [P=0.005; HR: 1.110 (95% CI: 1.032-1.193)], hypoxia [P=0.031; HR: 1.372 (95% CI: 1.029-1.830)] and nephrotoxicity [P<0.001; HR: 2.494 (95% CI: 1.566-3.972)] were indicated to be significant prognostic factors in multivariate analysis.

Table 2. Distribution of Comparative Variables among PCA⁺ and PCA⁻ Groups

	PCA⁺ Group n=157	PCA⁻ Group n=295	*P* Value
Age (years) [median (range)]	29 (16-65)	38 (15-67)	<0.001
Neutrophil Engraftment (days) [median (range)]	17(10-43)	16 (7-29)	<0.001
Platelet Engraftment (days) [median (range)]	16.5 (0-89)	14 (0-64)	<0.001
Red Blood Cell Transfusion (units) [median (range)]	4 (0-50)	3 (0-33)	0.005
Platelet Transfusion (units) [median (range)]	6 (0-75)	4 (0-63)	<0.001
Duration of Febrile Neutropenia (days) [median (range)]	5(0-52)	3(0-28)	<0.001
Duration of Hospitalization (days) [median (range)]	32 (16-130)	29 (9-94)	<0.001
Maximum Pain Score (points) [median (range)]	8 (0-10)	4 (0-10)	<0.001
Myeloablative Conditioning Regimen [n(%)]	124 (79)	152 (51.5)	<0.001
Total Body Irradiation [n(%)]	67 (42.7)	42 (14.2)	<0.001
Methotrexate Administration [n(%)]	153 (97.5)	226 (76.6)	<0.001
Sinusoidal Obstruction Syndrome [n(%)]	57 (36.3)	40 (13.6)	<0.001
Total Parenteral Nutrition [n(%)]	120 (76.4)	73 (24.8)	<0.001
Duration of parenteral nutrition (days) [median (range)]	11 (2-46)	8 (2-32)	0.031
Invasive Fungal Infection [n(%)]	60 (38.2)	59 (20)	<0.001

Table 3: Comparison of Toxicity Profiles between PCA⁺ and PCA⁻ Groups Based on NCI Common Toxicity Criteria

	PCA⁺ Group (n=157)	PCA⁻ Group (n=295)	*P* Value
Mucositis [median (range)]	4 (0-4)	1 (0-4)	<0.001
Febrile Neutropenia [median (range)]	2 (0-4)	2 (0-4)	<0.001
Infection [median (range)]	3 (0-4)	3 (0-4)	<0.001
Nausea [median (range)]	1 (0-3)	0 (0-3)	0.01
Vomiting [median (range)]	2 (0-4)	1 (0-4)	0.01
Diarrhea [median (range)]	1 (0-4)	0 (0-4)	<0.001
Constipation [median (range)]	0 (0-4)	0 (0-3)	0.001
Hypoxia [median (range)]	0 (0-4)	0 (0-4)	0.03
Bleeding [median (range)]	0 (0-4)	0 (0-2)	<0.001
Neurotoxicity [median (range)]	0 (0-3)	0 (0-3)	0.003
Hepatotoxicity [median (range)]	1 (0-4)	0 (0-3)	0.001
Nephrotoxicity [median (range)]	0 (0-4)	0 (0-4)	0.03

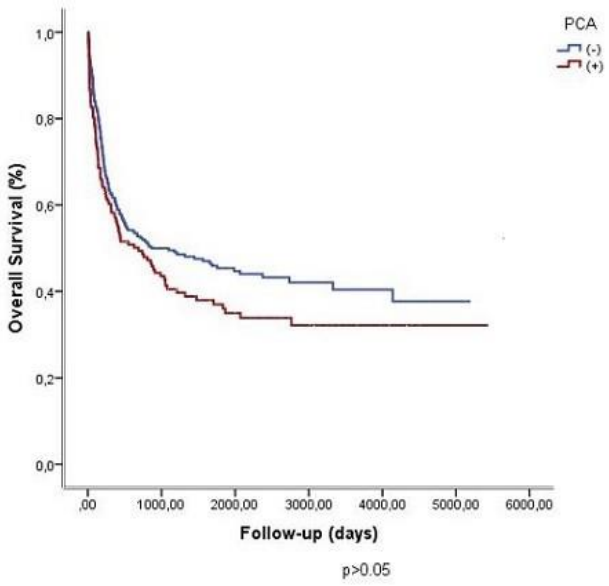

Figure 1. Probability of Overall Survival in PCA⁺ and PCA⁻ Groups (33.2% vs 37.7%) (p>0.05)

Table 4. Prognostic Risk Factors for Survival in Univariate Analysis

Risk Factors	*P* Value	Hazard Ratio	95% Confidence Interval
Pretransplant disease status	<0.001	1.44	1.28-1.62
ECOG performance status	<0.001	2.57	2.01-3.3
EBMT score	<0.001	1.26	1.12-1.43
Mismatched donor	0.02	1.46	1.05-2.02
Pretransplant CRP	<0.001	1.00	1.00-1.01
Pretransplant ferritin	<0.001	1.00	1.00-1.00
ATG for GvHD prophylaxis	0.03	0.6	0.39-0.94
Sinusoidal obstruction syndrome	<0.001	2.15	1.64-2.83
Defibrotide treatment for SOS	<0.001	1.46	1.27-1.69
Thrombotic microangiopathy	0.04	2.78	1.03-7.49
Infused $CD34^+$ cell count	0.04	0.89	0.81-0.99
Red blood cell transfusion	<0.001	1.04	1.02-1.05
Platelet transfusion	<0.001	1.02	1.01-1.03
Total parenteral nutrition	<0.001	1.82	1.43-2.33
Mucositis	<0.001	1.16	1.07-1.27
Febrile neutropenia	0.002	1.29	1.10-1.51
Duration of Febrile Neutropenia	<0.001	1.04	1.02-1.05
Infection	<0.001	1.26	1.12-1.43
Invasive fungal infection	<0.001	1.52	1.27-1.82
Diarrhea	0.02	1.13	1.02-1.26
Hypoxia	<0.001	1.57	1.45-1.71
Bleeding	0.002	1.38	1.12-1.70
Pscycological toxicity	<0.001	1.42	1.18-1.71
Neurotoxicity	0.02	1.46	1.06-2.02
Hepatotoxicity	<0.001	1.4	1.24-1.59
Nephrotoxicity	<0.001	1.72	1.55-1.92

ATG Anti-thymocyte Globulin; CRP C Reactive Protein; ECOG Eastern Cooperative Oncology Group; EBMT European Society for Blood and Marrow Transplantation; GvHD Graft versus Host Disease; SOS Sinusoidal Obstruction Syndrome

Discussion

In this study, the potential role and tolerability of opioid administration for mucositis-related-pain were investigated in a retrospective cohort of alloHCT recipients. Intensive conditioning, TBI administration and methotrexate use were shown to potentiate opioid requirement. Febrile neutropenia, IFIs and SOS were found to be more common in patients who received opioids with PCA. Discharge from hospital was delayed in the same group of patients. Early complications including hypoxemia, neurotoxicity, hepatotoxicity and nephrotoxicity were more frequently observed in PCA+ patients. Opioid administration with PCA did not represent a significant impact on OS.

Conditioning regimen is one of the most important factors for the development of mucositis in the early course of alloHCT. The intensity of the preparative regimen has a direct impact on epithelial cell damage [5-7]. Eduardo et al showed that myeloablative doses of busulfan may result in more frequent and long lasting mucositis [19]. Current study confirms and underlines the association of the conditioning regimen with the severity of mucositis and mucositis associated pain. As mucositis was more severe in patients who received MAC regimen, opioid and TPN requirement were more frequent in the same group of patients as expected. The frequency and grade of mucositis were found to be higher in patients who received methotrexate for GvHD prophylaxis. Leucovorine, which was not routinely used in our patients, was shown to shorten the duration of mucositis, neutrophil engraftment and hospital stay in previous reports [4,20]. Methotrexate may also prolong the healing process of mucositis in these patients [4,6,7,21]. In our study, patients who received methotrexate represented an increased requirement for opioid support which was potentially attributed to severe mucositis. Therefore, less toxic regimens for conditioning and GvHD

prophylaxis may help to reduce the frequency and severity of mucositis, as well as opioid requirement.

Total body irradiation has a significant role in early transplant related complications including mucositis [6,21-23]. In a study by Anand et al, the incidence and severity of mucositis were reduced in patients who received low dose TBI. In addition, TPN and opioid analgesics were more frequently used in patients with severe mucositis. Duration of hospitalization was significantly longer in the same group of patients [21]. In our study, opioid administration was more common in patients who were treated with TBI, independent from the dosing schedule. Similarly, the duration of TPN was significantly longer in PCA+ group. As maintenance of enteral nutrition is essential for the prevention of TPN related complications, appropriate and effective pain palliation can be lifesaving in these circumstances [4,7,21,23].

The association of age and mucositis was pronounced in several studies indicating that mucositis may be more severe and prolonged in younger patients which is also confirmed in the present study [1,24]. Nevertheless, this association was mainly attributed to the predominant use of MAC regimens in young and fit patients. On the contrary, as RIC regimens are generally preferred in relatively fragile elderly population with comorbidities, early transplant complications due to conditioning toxicity are expected to be lower in this group of patients.

Infections are important causes of non relapse mortality in the early posttransplant course. Delayed engraftment, which was also found to be associated with severe mucositis in the present study, may have a major role in the development of severe infections. Studies have shown that infectious morbidity was higher in patients with severe mucositis in concordance with our results which underline the potential intercourse between neutrophil engraftment and recovery of mucositis. In the present study, SOS was also found to be more frequent in patients who received opioids with PCA. Intensive conditioning regimens may cause a significant tendency for the development of preengraftment complications including mucositis and SOS, since they share a similar etiopathology mainly based on endothelial cell damage [2,3,25,26].

On the other hand, the association of opioid administration and early transplant toxicities including hypoxia, bleeding, neurological, hepatic and renal complications, may be attributed to the underlying conditions and comorbidities which may generate an additional risk for the development of severe toxicities. Nevertheless, transplant physicians should be aware of the potential drug side effects and/or interactions although average opioid dose is considered to be relatively lower and tolerable with PCA than standard methods [2,7,27].

Several studies have shown that hospitalization may be prolonged in patients with severe mucositis [10,25,28]. In a study by McCann et al, the length of hospital stay was found to be associated with a variety of factors including age, poor performance status, severe mucositis and delayed neutrophil engraftment [25]. Vera-Llonch et al demonstrated a significant relationship between the severity of mucositis and the length of hospital stay [28]. In concordance with these previous reports, duration of hospitalization was also found to be significantly longer in PCA+ group in the present study, which may be associated with the higher frequency of transplant related complications in this group, such as prolonged mucositis.

Although there are several reports which represented the prognostic impact of mucositis in transplant candidates, any significant association of mucositis with OS was not shown in the present study [5,29]. Mucositis was indicated to be a significant prognostic factor in univariate analysis, however the significance was not confirmed in multivariate analysis. Despite relatively large cohort of patients included, heterogeneity of the study population may be a

potential explanation for the lack of survival effect.

Despite the association of opioid administration with serious posttransplant complications, any significant impact of opioid use on OS was not demonstrated. This fact may draw attention to a potential additive role of opioid administration on transplant complications rather than being the primary underlying cause. Nevertheless, multifactorial nature of the milieu, as well as complex microenvironmental background, should also be taken into account in order to generate a more global and accurate vision for the development of posttransplant toxicities.

Based on the presented results, early and prompt treatment of mucositis and optimal supportive care including maintenance of oral hygiene, local and systemic measures for pain palliation, may prevent consecutive associated complications and improve quality of life in the early posttransplant setting. Reduced intensity conditioning, fractionated and low dose TBI, less toxic regimens for GvHD prophylaxis and integration of new therapeutic approaches which may overcome or compensate drug side effects may not only prevent mucositis and related complications, but also reduce the necessity for further recovery attempts.

In conclusion, opioid administration with PCA may be considered as an easy, safe and humanistic procedure with a tolerable side effect profile compared to its alternatives, particularly in patients who are exposed to intensive regimens and predicted to have a tendency for severe transplant related complications. The intensity of the conditioning should be determined based on a highly selected list of contributing factors including patient, disease and transplant characteristics. In consideration with its potential toxicity profile, pain palliation with PCA remains to be a privileged attempt to improve patient's quality of life in the early posttransplant course.

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