Antiemetic prophylaxis in patients undergoing hematopoietic stem cell transplantation: a multicenter survey of the Gruppo Italiano Trapianto Midollo Osseo (GITMO) transplant programs

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ABSTRACT

A survey within hematopoietic stem cell transplant (HSCT) centres of the Gruppo Italiano Trapianto Midollo Osseo (GITMO) was performed in order to describe current antiemetic prophylaxis in patients undergoing HSCT. The multicentre survey was performed by questionnaire, covering the main areas on chemotherapy induced nausea and vomiting (CINV): antiemetic prophylaxis guidelines used, antiemetic prophylaxis in different conditioning regimens, methods of CINV evaluation. The survey was carried out in November 2015 [before the publication of the Multinational Association of Supportive Care in Cancer (MASCC)/ European Society for Medical Oncology (ESMO) specific guidelines on antiemetic prophylaxis in HSCT] and its was repeated six months later. The results show a remarkable heterogeneity of prophylaxis among the various centers and a significant difference between the guidelines and the clinical practice. In the main conditioning regimens, the combination of a serotonin$_3$ receptor antagonist (5-HT$_3$-RA) with dexamethasone and neurokin$_1$ receptor antagonist (NK1-RA), as recommended by MASCC/ESMO guidelines, increased from 0-14% (before the publication of the guidelines) to 10-25% (after the publication of the guidelines). This study shows a lack of compliance with specific antiemetic guidelines, resulting mainly in under-prophylaxis. Concerted strategies are required to improve the current CINV prophylaxis, to draft shared common guidelines and to increase the knowledge and the adherence to the current recommendations for CINV prophylaxis in the specific field of HSCT.

INTRODUCTION

Over the past years, the attention on antiemetic prophylaxis in patients undergoing hematopoietic stem cell transplantation (HSCT) has considerably increased due a series of factors, including the following: recent research on chemotherapy-induced nausea and vomiting (CINV) physiopathology, distinguishing between acute and delayed physiopathology [1-7]; the possibility to use new phase-specific molecules for antiemetic prophylaxis [8-10]; and the ever growing concern about the “quality of life” of transplanted, and overall onco-hematological patients [11]. As a matter of fact, CINV cases after HSCT are among the most distressing side effects, in addition to the negative impact they create on patients’ quality of life. Finally, such concern was also determined by the lack of specific guidelines for transplanted patients until 2017, when MASCC/ESMO published, for the first time, specific guidelines for the patients undergoing HSCT [12,13].

These guidelines recommend a combination of a triple association serotonin$_3$-receptor antagonist (5HT$_3$-RA)RA with dexamethasone and a neurokin$_1$ receptor antagonist (NK1-RA). Previous guidelines did not provide a specific CINV prophylaxis for patients receiving HSCT. The 2015 National Comprehensive Cancer Network (NCCN) guidelines[14] recommended either a combination of a 5HT$_3$-RA with dexamethasone and a NK1-RA, the combination of netupitant/palonosetron (NEPA) and dexamethasone, or the combination of olanzapine with dexamethasone and a NK1-RA for patients receiving high emetic risk chemotherapy. Also, the latest 2017 ASCO guidelines[15] did not state a specific CINV prophylaxis for patients undergoing HSCT .

In order to investigate current clinical practice within Gruppo Italiano Trapianto Midollo Osseo (GITMO) transplant centres regarding the antiemetic prophylaxis in the principal condition regimens and the adherence to the international literature pertaining to antiemetic prophylaxis, a questionnaire-based survey was created and completed before and after the publication of the MASCC/ESMO specific guidelines for HSCT. This paper presents the results of this survey and also a discussion on the implications of this practice**.**

METHODS

Invitation to participate in the survey was emailed to the transplant directors of 50 centres that are part of the GITMO; the response rate was 86% of the interviewed centers. The questionnaire was placed on a web platform, and a database was created to facilitate data collection. The questionnaire was anonymous. The first survey was sent during the period from November to December 2015 before the publication of MASCC guidelines. A second survey was sent in the period March-May 2016 after the publication of MASCC guidelines. The questions covered the following topics: antiemetic prophylaxis guidelines used, antiemetic prophylaxis in the principal conditioning regimen, methods of CINV evaluation, medical perception of impacts on patients' quality of life and the extent of the CINV problem.

RESULTS

Tab. 1 shows the characteristics of the transplant centres responding to the survey. The majority (72%) are transplant centres for adult patients and perform both autologous and allogeneic transplants (82%), with just 18% performing exclusively autologous transplantation. After the publication of the MASCC/ESMO guidelines, 42% of the centers reported adherence to these guidelines, 40% of centers reported that they had internal CINV prophylaxis guidelines and only 18% reported that they followed other international guidelines (NCCN and ASCO), which are not specific for HSCT (**Tab. 2**). Fifty-five per cent of transplant centres use the "Commmon Terminology Criteria for adverse events"(CTCAE) for the evaluation of vomiting and 47% for nausea. However, only 4% and 25% of transplant centers use Functional Living-Index Emesis Score and visual analogue scale to evaluate nausea, respectively. As for the use of dexamethasone, only 18% of transplant centers use dexamethasone in all patients, while 16% do not use dexamethasone in any patient; the most administered dose (in 38% of transplantation centers) was 16 mg per day. The NK1-RA were used in all patients in 15% of transplant centers (10% before the publication of the MASCC/ESMO guidelines), but 30% of transplant centers do not use NK1-RA in any patient (56% before the publication of the guidelines). As for the second generation $5HT_3$-RA (palonosetron), 18% use the palonosetron in all patients, while 48% of centres do not use palonosetron **(Tab.3)**.

Analysing the main conditioning regimens of autologous transplantation (**Tab. 3**), figures show that the most used antiemetic prophylaxis, in the Melphalan 200 mg/m^2 regimen, after the publication of guidelines, is $5HT_3$-RA plus dexamethasone (45% of patients), while the triple combination of $5HT_3$-RA, dexamethasone and NK1-RA is only administered in 30% of patients (15% before the publication of the MASCC/ESMO guidelines). For the BEAM/FEAM/TEAM/BeEAM conditioning regimen, the most used antiemetic prophylaxis is $5HT_3$-RA plus dexamethasone (50 % of patients), while only 30% of patients are given the triple combination of $5HT_3$-RA, dexamethasone and NK1-RA (10% before the publication of the guidelines). The survey performed after the publication of the MASCC/ESMO guidelines regarding the antiemetic prophylaxis during the conditioning regimens of allogeneic transplantation showed that $5HT_3$-RA given alone is the most used prophylaxis in the regimens of tiothepa, fludarabine and cyclophosphamide (42% of patients), busulphan and cyclophosphamide (42% of patients), busulphan and fludarabine (51% of patients), total body irradiation and cyclophosphamide (41%), TBF(48% of patients) and cyclophosphamide (43% of patients)(**Tab. 4**). The use of dexamethasone in allogeneic transplantation ranges from 41% (tiotepa, busulphan and fludarabine conditioning regimen) to 60% (in the TBI plus cyclophosphamide conditioning regimen) and the most used dose of dexamethasone (in 38% of centers) is 16 mg die. The triple

combination of $5HT_3$-RA, dexamethasone and NK1-RA was reported in 15% of cases treated with tiothepa, fludarabine, cyclophosphamide, 25% with busulphan and cyclophosphamide, 20 % with busulfan and fludarabine, 19% with TBI and cyclophosphamide, 10% with TBF and 12% with cyclophosphamide. Overall, in all conditioning regimens (autologous and allogeneic), the combination of a 5-HT_3 receptor antagonist with dexamethasone and NK1-RA, as recommended by MASCC/ESMO, increased from 0-14% (before the publication of the guidelines) to 10-30% (after the publication of the guidelines).

A significant number of centres (66%) reported that CINV had a deleterious impact on quality of life and 65% reported an optimal response to CINV prophylaxis.

DISCUSSION

Our study, in which every effort was made to reflect the reality of clinical practice, shows that the problem of CINV in stem cell transplant recipients is far from being solved. Our survey describes CINV prophylaxis practices in 50 hematopoietic stem cell transplant centers, all of which are members of the GITMO. This analysis suggests that in Italy, the proportion of patients that, in routine practice, received MASCC/ESMO guidelines-consistent antiemetic prophylaxis is only a minority. In fact, only a percentage of patients between 10% and 25%, depending on the different conditioning regimen, received the triple prophylaxis with dexamethasone, NK1RA, and $5HT_3$RA. Moreover, about half of the centers use the "Common Terminology Criteria for adverse events" to assess nausea and vomiting, a very low percentage (25%) uses a visual analogue scale for nausea and similarly only 4% use the Functional Living-Index emesis score. This indicates the healthcare workers' poor perception of the CINV problem from the patients' perspective. In recent years, phase III studies have been published regarding the use of modern three-drug antiemetic prophylaxis for patients undergoing HSCT. A double-blind phase III [16] study randomized 181 patients to ondansetron and dexamethasone with or without aprepitant given on each day of the high-dose preparative regimen. The study showed a significant reduction in emesis without increasing toxicity or use of rescue medication in patients receiving aprepitant. The CR rate was 82% with the aprepitant arm versus 66%, however, there was no effect in the overall visual analog scale (VAS). The efficacy of aprepitant in patients with multiple myeloma undergoing high-dose chemotherapy with autologous SCT was investigated in phase II [17] and phase III clinical studies [18]. In the phase III study, patients with multiple myeloma were randomized to receive

either aprepitant administered at a dose of 125 mg orally on day 1 and 80 mg orally on days 2 to 4, granisetron and dexamethasone or matching placebo, granisetron and dexamethasone. The CR rate was significantly higher in the aprepitant arm compared to the control group (58 vs 41%); absence of major nausea (94 vs 88%) and vomiting (78 vs 65%) within 120 hours was significantly improved by aprepitant. Svanberg et al[17] randomized 96 patients to the 5-HT_3 receptor antagonist and dexamethasone with or without aprepitant for 7 days following HDCT and autologous SCT. Thirty-eight patients in the triple therapy regimen had no vomiting compared to 16 patients in the control group, and this difference was statistically significant. On the basis of these three studies the MASCC/ESMO[13] for the first time recommended a combination of 5-HT_3receptor antagonist with dexamethasone and aprepitant (NK1-RA) before chemotherapy for HSCT. Moreover, numerous studies have been published on the triple prophylaxis (dexamethasone, $5HT_3$-RA and NK1-RA) for CINV in both autologous and allogeneic transplantation [19-25], showing a greater effectiveness compared to the combination of dexamethasone and $5HT_3$-RA.

This survey demonstrates that in "real life" the adherence to antiemetic MASCC guidelines is very low for the main conditioning regimens; in fact, in the autologous setting the proportion of patients who received the triple prophylaxis with dexamethasone, NK1-RA, $5HT_3$-RA, is only 30% for melphalan (200 mg/m^2), 30 % for BEAM/TEAM/BeEAM/FEAM; in allogeneic setting 25% for busulphan and cyclophosphamide, 19% for TBI and cyclophosphamide, 10% for TBF and 15% for thiotepa, cyclophosphamide and fludarabine. Various factors may have contributed to the low percentage (15%) of centers using NK1-RA in all patients. First of all, the registered schedule of aprepitant (125 mg on the first day and 80 mg on the second and third day) may not be considered suitable for multiday therapy like most conditioning regimens. Furthermore, there may be concerns for pharmacological interference during the conditioning regimen as aprepitant is an inhibitor of CY3A4 which may increase the AUC of dexamethasone [26] and, in the survey, in 38% of transplant centers a dose of dexamethasone of 16 mg per day was used, a high dose that could create problems especially in the setting of allogeneic transplantation. The same plasma concentration of aprepitant may also increase with the use of CY3A4 inhibitor drugs, such as, voriconazole, posaconazole. Moreover, since the addition of NK1-RA has been highly recommended for HSCT in the last updating on the antiemetic guidelines and it was optional in the previous versions, it will take more time to change the clinical practice of the HSCT centres. Finally, there may be difficulties in the prescription of NK1-RA (aprepitant or NEPA) in HSCT setting, which have to be registered with the Italian Medicin Agency (AIFA) for the CINV prophylaxis in high emetogenic chemotherapy with cisplatin or in moderately emetogenic

chemotherapy. These aspects are likely to have a negative influence on the adherence to guidelines. The Pan European Emesis Registry (PEER) study demonstrated that the use of guidelines-consistent CINV prophylaxis resulted in a greater proportion of patients achieving complete response to CINV, as compared to guideline-inconsistent CINV prophylaxis[27]. Moreover, the ISPIRE study [28] showed that the increased adherence to antiemetic guidelines could significantly reduce the incidence of CINV after high and moderately emetogenic chemotherapy. The implementation of specific guideline recommendations for CINV prophylaxis could be considered as a means to reduce the burden of CINV. The results of this survey are particularly useful for two reasons. First, this is not an interventional study, and, therefore, the results are a picture of the real world, and reproduce the wide variations of CINV prophylaxis. Second, the research highlights how the majority of the transplant centres (66%) are aware of the CINV negative effects on patients' quality of life, yet only 42% of them stick to international specific guidelines to deal with such an important matter. In conclusion this survey shows that there is a lack of compliance with antiemetic guidelines; the main observation is that there is an underprophylaxis. This gap between guidelines and current practice should be urgently filled up either sensitizing transplant physicians and nurses to advances in CINV prophylaxis or promoting specific clinical research for HSCT patients.

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Tab.1 Characteristics of the 43 transplant centres responding to the survey

Patient group	
Adult only	**72%**
Pediatric only	**18%**
Both adult and pediatric	**10%**
Transplant type performed	
Autologous	**18%**
Autologous and allogeneic	**82%**

Tab.2

Questions	
Which CINV prophylaxis guideline does your institution follow?	o **MASCC/ESMO guidelines 42%** o Internal guidelines 40% o NCCN/ASCO guidelines 18%
In your Center, do you use the "Common Terminology Criteria for adverse events" to evaluate vomiting?	o **Yes 55%** o No 45%
In your Center, do you use the "Common Terminology Criteria for adverse events" to evaluate nausea?	o **No 53%** o Yes 47%
In your Center, do you use the Functional Living-Index emesis score?	o **No 96%** o Yes 4%
In your Center, do you use the visual analogue scale to evaluate nausea?	o **No 75%** o Yes 25%
In your Center, do you use dexamethasone?	o In 0% of patients 16% o **In 25% of patients 34%** o In 50% of patients 14% o In 75% of patients 18% o In all patients 18%

What dexamethasone daily dose is recommended in your institution's CINV prophylaxis?	o **16 mg** **38%** o 8 mg 30% o 12 mg 20% o 20 mg 12%
In your Center, do you use NK1-RA?	o **In 0% of patients** **30%** o In 25% of patients 20% o In 50% of patients 20% o In 75% of patients 15% o In all patients 15%
In your Center, do you use Palonosetron?	o **In 0% of patients** **48%** o In 25% of patients 22% o In 50% of patients 8% o In 75% of patients 4% o In all patients 18%

Tab. 3 CINV prophylaxis in autologous conditioning regimens

Questions	Before MASCC/ESMO 2016	After MASCC/ESMO 2016
Which CINV prophylaxis do you use in melphalan conditioning regimen (200 mg/m^2)?	**5HT$_3$RA+Dexa 45%** 5HT$_3$RA+Dexa+NK1RA 15% 5HT$_3$RA 30% 5HT$_3$RA+NK1RA 10%	**5HT$_3$RA+Dexa 45%** 5HT$_3$RA+Dexa+NK1RA 30% 5HT$_3$RA 22% 5HT$_3$RA+NK1RA 3%
Which CINV prophylaxis do you use in BEAM/FEAM/BeEAM/ TEAM conditioning regimen?	**5HT$_3$RA+Dexa 45%** 5HT$_3$RA+Dexa+NK1RA 10% 5HT$_3$RA 30% 5HT$_3$RA+NK1RA 15%	**5HT$_3$RA+Dexa 50%** 5HT$_3$RA+Dexa+NK1RA 30% 5HT$_3$RA 15% 5HT$_3$RA+NK1RA 5%

Tab.4 CINV prophylaxis in allogeneic conditioning regimens

	Before MASCC/ESMO 2016	After MASCC/ESMO 2016
Which CINV prophylaxis do you use in thiotepa, fludarabine, cyclophosphamide reduced intensity conditioning regimen?	**$5HT_3$ RA 42%** $5HT_3$ RA +Dexa 35% $5HT_3$RA + NK1RA 23%	**$5HT_3$ RA 42%** $5HT_3$ RA +Dexa 31% $5HT_3$RA + NK1RA 10% $5HT_3$RA+Dexa+NK1RA 15%
Which CINV prophylaxis do you use in busulphan plus cyclophosphamide conditioning regimen?	**$5HT_3$RA+ Dexa 48%** $5HT_3$RA 42% $5HT_3$RA+NK1RA 10%	**$5HT_3$RA 42%** $5HT_3$RA + Dexa 24% $5HT_3$RA+Dexa+NK1RA 25% $5HT_3$RA+NK1RA 9%
Which CINV prophylaxis do you use in busulphan plus fludarabine regimen?	**$5HT_3$RA 42%** $5HT_3$RA+Dexa 30% $5HT_3$RA+NK1RA 28%	**$5HT_3$RA 51%** $5HT_3$RA+Dexa 25% $5HT_3$RA+Dexa+NK1RA 20% 5HT3RA+NK1RA 4%
Which CINV prophylaxis do you use in TBI plus cyclophosphamide conditioning regimen?	**$5HT_3$RA+Dexa 49%** $5HT_3$RA 21% $5HT_3$RA+NK1RA 16% $5HT_3$RA+Dexa+NK1RA 14%	**$5HT_3$RA+Dexa 51%** $5HT_3$RA+Dexa+NK1RA 19% $5HT_3$RA 16% $5HT_3$RA+NK1RA 14%
Which CINV prophylaxis do you use in TBF conditioning regimen?	**$5HT_3$RA+Dexa 33%** $5HT_3$RA 32% $5HT_3$+NK1RA 27% $5HT_3$+Dexa+NK1RA 8%	**$5HT_3$RA 48%** $5HT_3$RA+Dexa 31% $5HT_3$RA+Dexa+NK1RA 10% $5HT_3$RA+NK1RA 11%
Which CINV prophylaxis do you use in CTX (200 mg/m^2)?	**$5HT_3$RA+Dexa 45%** $5HT_3$ RA 36% $5HT_3$+Anti NK1 19%	**$5HT_3$RA 43%** $5HT_3$ RA +Dexa 31% $5HT_3$RA+Dexa+NK1RA 12% $5HT_3$RA+NK1RA 14%

Tab.5

Conditioning regimen	Compliance with 2016 MASCC/ESMO guidelines
Melphalan (200 mg/m^2)	30 %
BEAM/FEAM/BeEAM/TEAM	30 %
Thiotepa, Fludarabine, cyclophosphamide(RIC)	10%
Busulphan plus cyclophosphamide	25%
Busulphan plus fludarabine	20%
TBI plus cyclophosphamide	19%
TBF	10%
CTX (200 mg/m^2)	12%