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**This is the author's manuscript**

*Original Citation:*

*Availability:*

This version is available <http://hdl.handle.net/2318/155818> since 2020-06-17T15:23:51Z

*Published version:*

DOI:10.1007/s00520-014-2227-y

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This is the author's final version of the contribution published as:

Gonella S; Berchialla P; Bruno B; Di Giulio P.. Are orange lollies effective in preventing nausea and vomiting related to dimethyl sulfoxide? A multicenter randomized trial. SUPPORTIVE CARE IN CANCER. 22 (9) pp: 2417-2424. DOI: 10.1007/s00520-014-2227-y

The publisher's version is available at:

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**Title of the paper**

Are orange lollies effective in preventing nausea and vomiting related to Dimethyl Sulfoxide? A multicenter randomized trial

**Running title**

Orange lollies efficacy in preventing nausea DMSO related

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## **Abstract**

*Purpose* Nausea and vomiting (NV) related to DMSO affect patients undergoing auto-SCT despite anti-emetic measures. Orange flavoring may reduce gastrointestinal symptoms.

*Methods* A multicenter, randomized, three-arm, open-label trial in four Italian large bone marrow transplant centers was conducted to assess the effectiveness of orange aroma in preventing NV related to DMSO. Patients were randomized to orange ice lollies, Non-citrus ice lollies and routine treatment (deep breaths) during reinfusion. Data on NV were collected up to 5 days after infusion. Sixty-nine/98 patients were randomized: 23 to orange, 21 to Non-citrus ice lollies and 25 to routine treatment.

*Results* Although in the 48 hours after transplantation no differences were observed in controlled nausea (Numeric Rating Scale 0-100 (NRS)  $\leq 25$ ) or vomiting, significantly fewer patients had no episodes of vomiting, no anti-emetic rescue therapy and no nausea (NRS  $< 5$ ) in the deep breath vs lollies groups ( $p = 0.017$ ). The intensity of nausea over time differed significantly between ice lollies vs routine care ( $p = 0.001$ ) groups, but not between the orange and Non-citrus groups ( $p = 0.428$ ).

*Conclusion* The vasoconstrictive action of ice may prevent NV related to DMSO in the acute phase and reduce the need for rescue anti-emetic therapy. Ice lollies offer a simple, non-invasive and economic means for relieving nausea and vomiting related to this preservative.

**Keywords** Nausea • Vomiting • Hematopoietic stem cell transplantation • Cryopreservation • Dimethyl Sulfoxide • Aromatherapy

## Introduction

Hematopoietic stem cell transplantation (HSCT) is standard treatment for many patients with congenital or acquired disorders of the hematopoietic system or with chemo-, radio- or immuno-sensitive malignancies [1]. World-wide, 50 417 HSCTs were done in 2006, 21 516 allogeneic (43%) and 28 901 autologous (57%) [1].

For auto-SCT, hematopoietic stem cells (CD34 +) are slowly frozen and stored in liquid nitrogen at -196°C with DMSO, that reduces cellular dehydration and osmotic stress [2]. Reinfusion may have several side effects such as hemolysis, anaphylactic reactions, kidney failure, high systolic and diastolic blood pressure, bradycardia. However, gastrointestinal problems are the most frequent, particularly nausea and vomiting (NV), partly related to the characteristic garlic-like breath due to pulmonary excretion of the cryopreservative [3, 4, 5, 6]. DMSO and its metabolites (dimethylsulfone and dimethylsulfide), are excreted over the 24 hours after infusion, through urine, skin and breathing [3]. The toxicity is proportional to the concentration and amount of DMSO [7] and increases with the number of bags and of cells harvested and with the patient's weight [2, 4, 6, 8]. A 10% solution is generally used [2, 3]; the 5% solution with lower incidence of side effects is not recommended for lengthy storage since its safety has been assessed only over a few months [9, 10].

Dimethyl sulfoxide may activate the vomiting center through the CTZ as soon as the agent is detected in the blood. This sensation may be compounded as it passes directly into the saliva and is then tasted and smelled upon entering the oral and nasal cavity [13]. Previous studies [14] showed that an unpleasant odor can be masked by a pleasant one presumably through lateral inhibitory connections in the local neuronal circuit of the olfactory bulb [18,19]. The incidence of nausea with DMSO may range between 50% and 80% [2]; older patients are less affected [6]. This variability is probably related to the individual threshold and to the emetogenic property of the conditioning regimen. No drug seems to relieve NV associated with DMSO [11] with its negative impact on quality of life and on the risk of anorexia, dehydration and electrolyte imbalance, up to renal failure [12]. Nausea, even mild, may negatively affect the quality of life in 25% of patients [12].

The smell and flavor of orange may reduce the patient's perception of its odor [5, 6] and thus NV (an unpleasant odor can be masked by a pleasant one [13, 14]) although studies have given conflicting results. This suggested the hypothesis that DMSO-evoked activity map (odor map) might be inhibited by activation of mitral cells in the neighboring orange-responsive clusters. Potter's three-arm trial [6] showed that orange slices and aromatherapy with orange fragrance during the reinfusion of autologous stem cells were more effective than deep breathing - the "gold standard" - for reducing nausea, while Ndao's double-blind, placebo-controlled trial [11] found no

benefit of respiratory aromatherapy with bergamot essential oil when added to standard supportive care. No studies explored the length of this inhibition, however we might suppose that it is longer than the effective masking-stimulus since Takahashi et al. [14] noted that, in many mitral-tufted cells, responses to odorants lasted for long period even after cessation of the odor stimulation.

The aims of the study were to assess the effectiveness of orange aroma in preventing DMSO-related NV and to measure the incidence of NV and need for anti-emetic rescue therapy in patients undergoing auto-SCT.

## **Methods**

### Study design and clinical setting

In this experimental, three-arm, open-label trial, patients undergoing auto-SCT were recruited in four large bone marrow transplant centers with more than 20 autologous transplantation/year in Piedmont (northern Italy) between June 2012 and January 2013. The study was approved by the ethics committees. All patients provided written informed consent.

### Patients

Ninety-eight patients were consecutively evaluated at entry and 69 (70%) were recruited (Figure 1). Patients older than 18 years, able to use the Numerical Rating Scale (NRS) 0-100 and to give consent were included. Patients with known or suspected allergy to (or dislike of) oranges or ice lollies, expected to require three or more bags of autologous stem cells, nausea or vomiting not controlled at the end of the conditioning phase, dental pain or hypersensitivity to cold were excluded.

### Study procedures

Patients were randomized to three groups by randomization in blocks with step 6 (ratio 1:1:1) stratified by center using the software randomization.com [20]. Treatment codes in sealed opaque envelopes.

Stem cells were stored in liquid nitrogen at  $-196^{\circ}\text{C}$  with 10% DMSO. Bags were thawed at

37°C and reinfusion started within a few minutes. All patients received premedication with steroids and during reinfusion were encouraged to breathe deeply (inhaling through the nose and exhaling through the mouth to expel DMSO). One group was randomized to orange ice lollies during reinfusion (Orange group), another to Non-citrus lollies (Non-citrus group) and the third group to deep breaths (Only-breathing group). Lollies sucking started and ended with infusion. Ice lollies were chosen in place of other modalities (i.e orange in slices) to standardize the intervention and guarantee the administration of controlled quantity of orange aroma. Patients were given two ice lollies for each bag (the reinfusion lasts 10-15 min per bag and it takes 5-8 minutes to finish an ice lolly) and they were free to ask for more. In the pilot study the median consumption was 1.5 ice lollies [range 1-3] per bag. A nurse was present throughout the reinfusion.

We used commercial ice lollies with a 13-20% concentration of aroma and all Non-citrus fragrances except aniseed, which may be emetic [21]. Ice lollies were provided by the catering company or purchased by patients.

The following information was collected: (1) Patients' main demographic and clinical characteristics, underlying disease, previous transplantation (clinical records); recurrent headache ( $\geq 2$  episodes/week), history, previous chemotherapy-induced nausea and vomiting, motion or morning sickness (interview); self-administered Zung Self-Rating Anxiety Scale (SAS) [22]. This consists of 20 items on a four-point scale (from a little to most of the time). The SAS score was converted into an Anxiety index: scores  $\geq 45$  indicate anxiety; (2) Treatment: conditioning regimen, chemotherapy cycle, premedication and anti-emetic prophylaxis (clinical records); number of bags and number of ice lollies sucked during the reinfusion; (3) Side effects: nausea (NRS 0-100), vomiting (number of episodes), and vital signs before and after reinfusion; any adverse reactions during the reinfusion.

The emetogenic potential of conditioning cycles was evaluated with the Hesketh score and was comparable, except for melphalan 100 mg/m<sup>2</sup> [23].

From the transplantation day until day +5 each patient self reported every 4-hour: nausea intensity (NRS 0-100); vomiting and retching episodes; anti-emetic rescue therapy. The median

intensity of nausea was measured over 24 hours; the number of episodes of vomiting and retching and of doses of anti-emetic rescue therapy were recorded from the end of reinfusion.

In each ward an experienced nurse was instructed for data collection. Consultancy was available throughout the data collection period.

Nausea was considered absent if  $<5$ , controlled between 5 and 25 and not controlled if  $>25$  [12]. Vomiting and retching were recorded separately and considered controlled if  $\leq 2$  episodes (vomiting and retching) in the 24 hours before reinfusion [12] and  $\leq 1$  episode during reinfusion.

## Study outcomes

### Primary

Proportion of patients with controlled nausea (NRS  $\leq 25$ ) or vomiting

### Secondary

Proportion of patients with

1. no nausea (NRS  $<5$ ) or vomiting;
2. complete protection (no vomiting, no anti-emetic rescue therapy and controlled nausea);
3. total control (no vomiting, no anti-emetic rescue therapy and no nausea).

After reinfusion patients were assessed in up to 48 hours (early period), to account for possible delayed effects of DMSO, and in the total period (0-120 hours). Late phase refers to 48-120 hours after auto-SCT.

## Statistical analysis

Continuous variables were expressed as median and interquartile ranges and were compared between groups using the Kruskal-Wallis test. Categorical variables were summarized as sums and percentages and the  $\chi^2$  test with Yates' correction (or Fisher's exact test) was used for comparisons.

Correlation was assessed using the Spearman coefficient.



A generalized least-square regression model was used to ascertain whether the interaction between groups and time with respect to nausea intensity was significant [24]. A correlation structure was specified to account for repeated measures over time (24, 48, 72, 96 and 120 hours after reinfusion) on the same patient. A continuous-time autoregressive of order 1 (CAR1) correlation structure resulted in the best model fit, based on Akaike Information Criterion (AIC) values. Age, sex and number of stem cell bags infused were entered into the model. The linear relationship of nausea intensity over time was assessed using restricted cubic splines and tested with a Wald chi-square test.

The data were analyzed with R version 2.15 [25]. All p values are two-sided and significance less than 0.05 was considered significant. Analyses were performed by intention-to-treat.

#### Sample size

In the pilot study all patients in Orange lollies had controlled nausea or vomiting, 83% in Non-citrus lollies and 50% in only-breathing; with 23 patients in each group we can show, with 90% power, a 15% difference in the proportion with controlled nausea or vomiting 48 hours from auto-SCT, at a two-sided  $\alpha$  level of 0.05 with Bonferroni correction for multiple comparisons.

#### Results

Over 60% of patients were males and almost half were conditioned with melphalan 200 mg/m<sup>2</sup>. None had electrolyte imbalance or had been treated with radiotherapy (Table 1).

The number of patients with previous auto-SCT differed significantly among groups ( $P=0.005$ ), but the incidence of not controlled nausea or vomiting in the 48 hours post-transplant was similar in patients at the first vs second reinfusion (7.7 vs. 13.3%,  $P=0.458$ ).

Premedication and anti-emetic prophylaxis before reinfusion were given at standard doses; six patients received a 3-drug premedication (3 both in lollies and Only-breathing group) and ten a multidrug prophylaxis (6 in lollies and 7 in Only-breathing group). No patients were administered

drugs during infusion (table 2).

Sixteen patients (70%) in the Orange and 15 (71%) in the Non-citrus group had only one bag in 10 percent DMSO-cryopreserved PBSCs vs 21 (84%) of the Only-breathing group. Infusion rate ranged between 20 to 50 ml per minute throughout all the groups and reinfusion lasted about 12 minutes with one bag, 28 with two. The median consumption of ice lollies was 1.5 [range 1-2.5] in the Orange group and 1 [1-1.5] in the Non-citrus group.

Overall, vital signs remained stable during reinfusion, except for a slight increase in systolic blood pressure in the Orange group. Four patients reported an adverse event: a hypotensive crisis (Non-citrus and Only-breathing groups) and an episode of bradycardia (Orange and Non-citrus groups).

#### Nausea before, during and after reinfusion

Sixteen patients (80%) in the Orange and 14 (78%) in the Non-citrus group reported no nausea during reinfusion vs 15 (71%) of the Only-breathing group. The numbers of patients with uncontrolled nausea during transplantation were comparable, though slightly lower in the ice lollies groups. At the end of reinfusion 20 Only-breathing patients (83%) had no or controlled nausea vs 20 (95%) in the Non-citrus and 21 (91%) in the Orange group. In all, 23 patients (30%) did not report nausea.

In the first 48 hours, over 90% of ice lollies patients (21 (91%) in the Orange and 20 (95%) in the Non-Citrus group) had no or controlled nausea, compared to 76% (19) of the Only-breathing group. About 30% of patients randomized to ice lollies (8-35% in the Orange and 6-29%, in the Non-Citrus group) reported nausea  $\geq 5$  compared to over 60% (16) of the Only-breathing group.

Forty-eighth hours after infusion, 45 patients (65%) reported nausea which was uncontrolled in 9 (36%) Only-breathing, 7 (30%) Orange and 3 (14%) Non-citrus patients. Overall 24 had nausea  $> 25$  at least once in the five days after transplantation. Generally the nausea started to increase on the third day after reinfusion with a peak between 72 and 96 hours, decreasing on the fifth day. The

pattern for vomiting was similar. A borderline significant interaction ( $P=0.057$ ) emerged between treatment and time: nausea remained almost unchanged in Only-breathing patients; while initially lower in the ice lollies groups raised over the next few days, up to the level of the Only-breathing group on day 5.

Longitudinal regression analyses including treatment, age, sex, number of bags and hours from transplant showed a significant difference between the three treatments ( $P=0.0003$ ), as well as an average increase of 3.8 points in nausea intensity every 24 hours regardless of the treatment; female sex was a risk factor for nausea. Nausea intensity over time was significantly different between the ice lollies and Only-breathing ( $P=0.001$ ), but not between Orange and Non-citrus groups ( $P=0.428$ ).

The longitudinal regression model showed a significant reduction of nausea with age, and a rise with the number of bags infused. In the first 48 hours after transplantation median nausea was 2.1 [0-11.5] if one bag was infused and 10.4 [0-18.1] if two. No correlation was observed between weight and nausea control in the acute or delayed phase.

#### Vomiting before, during and after reinfusion

About a quarter of the patients (16, 23%) had at least one vomiting episode in the 24 hours before the transplant.

During transplantation six patients vomited in the Orange group and four in the other groups.

Similarly, in the first 48 hours almost all ice lollies patients had no or controlled vomiting (22/23 Orange and 20/21 Non-citrus group) vs 15/25 (60%) in the Only-breathing group.

Throughout the five-day observation period about half the patients who ate lollies reported at least one episode of vomiting (13 Orange and 11 Non-citrus group) compared to 80% (20) of the Only-breathing group.

#### Effectiveness of orange ice lollies

No significant difference in the primary endpoint (controlled nausea or vomiting) during reinfusion

( $P=1.000$ ) or in the following 48 hours ( $P=0.090$ ) was observed between groups, although in the two days post-transplant these symptoms were still controlled only in the ice lollies patients (93% controlled nausea and 96% controlled vomiting) vs 76% controlled nausea and 60% controlled vomiting in the Only-breathing group. Significant differences were observed for all secondary endpoints (Table 3). During the first 48 hours significantly fewer patients had no nausea or vomiting in the Only-breathing group vs ice lollies ( $p = .002$ ). In fact, patients with complete protection were more than double in the ice lollies group compared to Only-breathing ( $P =0.003$ ) and the pattern was similar for total control ( $P =0.017$ ).

#### Antiemetic rescue therapy

Twenty-three (30%) patients required anti-emetic rescue therapy but in the ice lollies groups from the third day and in the Only-breathing group already in the first 48 hours (Table 3). During the five days, five patients in the Orange, six in the Non-citrus and 12 in the Only-breathing groups required rescue therapy and respectively 10, 14 and 33 doses were given.

#### Discussion

This is the first study that assessed the effect of ice lollies in preventing DMSO-related NV in patients undergoing auto-SCT. Although we found no differences in controlled nausea or vomiting in the 48 hours post-transplant and though considering the delayed emetogenic effect of melphalan, over 90% of patients randomized to ice lollies had controlled nausea and almost all controlled vomiting ( $\leq 2$  episodes), compared to respectively 76% and 60% in the Only-breathing group. The advantage was observable in the first 48 hours [No nausea or vomiting in 89% ice lollies vs 52% Only-breathing patients ( $P=0.002$ )]; furthermore, 57% in the lollies groups had total control compared to 24% Only breathing ( $P=0.017$ ).

These findings suggest that ice lollies may have an anti-emetic effect and a larger sample would probably have shown statistically significant differences in the primary endpoint.

The effect of ice lollies on NV mechanisms seems related to the vasoconstriction or reduction of taste perception due to cold, more than to the orange aroma. In fact the proportions of patients with complete protection and total control were similar in the lollies groups; the differences for nausea intensity disappeared after adjustment for treatment, age, sex, number of bags and hours from transplant ( $P=0.428$ ), but remained when comparing with the Only-breathing group ( $P=0.001$ ). The lack of effect on reduction of nausea from inhaled aromatherapy was already shown in adolescents undergoing auto-SCT [11].

Gastrointestinal symptoms continue to be a problem in the first 48 hours despite anti-emetic prophylaxis: more than 40% of patients reported nausea, and 23 vomiting, in 16 cases despite no or controlled nausea, suggesting that the two symptoms are different, although related. In the first 48 hours only one patient in the ice lollies groups required anti-emetic rescue vs 11 in the Only-breathing group; the advantage was maintained despite comparable levels of delayed nausea.

After 48 hours symptom control was worse: more than 65% of patients reported nausea, not controlled in 42%, and about 60% had at least one episode of vomiting (80% in the Only-breathing group). The intensity of nausea increased with time (borderline significant interaction ( $P=0.057$ )): however, it cannot be attributed to DMSO, whose half-life is only 24-36 hours [2, 3], but, more likely to the mucositis whose preliminary symptoms are nausea and abdominal cramps [26]. Its incidence ranges between 75% and 85% and it usually arises 3 to 5 days after transplant [22, 23, 24, 25]. The delayed nausea may depend on P-dependent (Undecapeptide tachykinin acting as a sensory neurotransmitter in the central nervous system and as a local hormone in the gastrointestinal tract ,involved in pain and vomiting) mechanism and therefore it might be caused by cytotoxic therapy-induced mucosal damage (CIMD) [26]. Thus the nausea is initially linked to the cryopreservative and later to gastrointestinal mucosal damage [26].

The intensity of nausea increased with the number of bags infused [7]; female sex was confirmed as an independent risk factor for nausea ( $P=0.028$ ) and a likely predictor of Mucositis [27, 28].

Since the amount of stem cells needed (and the number of bags) increases with body weight, a parallel increase in nausea was expected in patients infused 2 bags: differently from Potter's study [6], we found no correlation. However, our population was hardly comparable to Potter's as only four patients (6%) weighed more than 90 kg compared to 27 (45%) in the American study.

### Strengths and limitations

The central randomization prevented a selection bias, and stratification by center avoided a center effect. A major strength of the study is the generalization of the results to Italian patients undergoing auto-SCT, since patients' main demographic and clinical characteristics and chemotherapy cycles are comparable across centres.

No data was lost due to the excellent patients' collaboration and intervention (administration of ice lollies) was more comparable than in previous studies [6]. The three-arm design allowed to assess whether the efficacy of the intervention was related to the vasoconstrictive action of ice or aroma.

The study was limited by its small sample size and the predominance of male patients, although the prevalence of auto-SCT is considerably higher in men [29, 30]. Moreover, we did not record the total dose of DMSO in mg/kg which can affect nausea and vomiting; however, 31 ice lollies patients (70%) (16 (70%) Orange and 15 (71%) Non-Citrus) had only one bag in DMSO-cryopreserved PBSCs vs 21 (84%) in the Only breathing group, thus the latter were overall less exposed to DMSO.

### Conclusion

Although no differences were observed for controlled nausea or vomiting, the results suggest the potential efficacy of ice in raising the proportion of patients with no nausea or vomiting due to DMSO and in reducing the need for anti-emetic rescue therapy. However, larger samples are needed to confirm whether the effect was due to the vasoconstrictive action of ice rather than the aroma itself, testing flavors in different forms (ice lollies, candies or lollipops).

The need of anti-emetic prophylaxis of conditioning cycles should be revised since half the patients came to the transplant day with uncontrolled nausea or vomiting.

**Acknowledgements** Our thanks to nurses for helping identify potential participants and for data collection, but especially the study participants who agreed to try the intervention even during a time of illness. This work was supported by Fondazione Neoplasie Sangue Onlus (FO.NE.SA).

**Conflict of interest** The authors have no conflict of interest to declare.

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**Table 1** Patients' main baseline characteristics

	Orange (n = 23)	Non-citrus (n = 21)	Only deep breathing (n = 25)	<i>P</i> value
Male (n/%)	17 (74)	12 (57)	14 (56)	0.371
Age years (median; IQR)	60 [52-64]	58 [53-62]	55 [49-64]	0.325
Weight kg (median; IQR)	70 [62-84]	74 [64-83]	69 [62-79]	0.719
Education (n)				0.135
Elementary school	3	-	2	
Junior school	8	7	6	
High school	7	7	14	
University	5	7	3	
History (n)				
Smoking	9	8	9	0.974
Hypertension	9	8	6	0.341
Previous CINV	9	3	10	0.144
Opioid therapy in progress	5	3	2	0.401
Recurrent headache	4	4	2	0.507
Anxiety	3	3	4	0.958
Motion sickness	2	2	4	0.687
Morning sickness	1	1	5	0.124
Diabetes	1	1	3	0.517
Ex-alcohol drinker	-	3	1	0.115
Dyslipidemia	1	1	1	0.684
Renal failure	2	-	1	0.161
Past drug addiction	1	1	-	0.115
Diagnosis (n)				0.707
MM/LNH/LAM/L. Plasmacellular/LH	19/2/1/1	12/5/1/-/1	14/3/2/4/1	
M. Waldstrom/L.Burkitt/reticulosarcoma		-/1/1	1	
Previous transplantation n (%)	12 (52)	3 (14)	15 (60)	0.005
Chemotherapy cycles (n)				0.297
Mel 100/Mel 200/FEAM/BEAM/M-VD/	6/12/3/-/-	4/7/8/-/1	3/13/3/1/3	
Bu-Cy/Ara-C+Idarubicina/D-PACE	1/-/1	1	1/1	
Myeloablative conditioning n (%)	16 (70)	15 (71)	19 (76)	0.712

Abbreviations: BEAM, bendamustine-etoposide-cytarabine-melphalan; Bu-Cy busulfan-cyclophosphamide; CINV, chemotherapy-induced nausea and vomiting; D-PACE, dexamethasone-cisplatin-adriablastin-cyclophosphamide-etoposide; FEAM, fotemustine-etoposide-cytarabine-melphalan; LAM, acute myeloid leukemia; LH, Hodgkin's lymphoma; NHL, Non-Hodgkin's lymphoma; Mel 100, melphalan 100 mg/m<sup>2</sup>; Mel 200, melphalan 200 mg/m<sup>2</sup>; MM, multiple myeloma; M-VD, velcade-melphalan-dexamethasone

**Table 2** Reinfusion premedication and anti-emetic prophylaxis

	Orange (n = 23)	Non-citrus (n = 21)	Only breathing (n = 25)
Premedication (n) <sup>a</sup>			
Methylprednisolone 125 mg + chlorphenamine 10 mg	19	17	20
Hydrocortisone 200 mg + chlorphenamine 10 mg	5	5	6
Hydroxyzine 25 mg	1	-	2
Antiemetic prophylaxis (n) <sup>a</sup>			
Ondansetron	20	19	23
Metoclopramide	4	3	2
Aprepitant	3	1	3
Chlorphenamine	1	-	2
Alizapride	1	-	-
Dexamethasone	-	-	1
Granisetron	-	-	1

<sup>a</sup> The sum is greater than the total because some patients received multidrug treatment

**Table 3** Effectiveness of interventions during auto-SCT and in the subsequent 48 hours

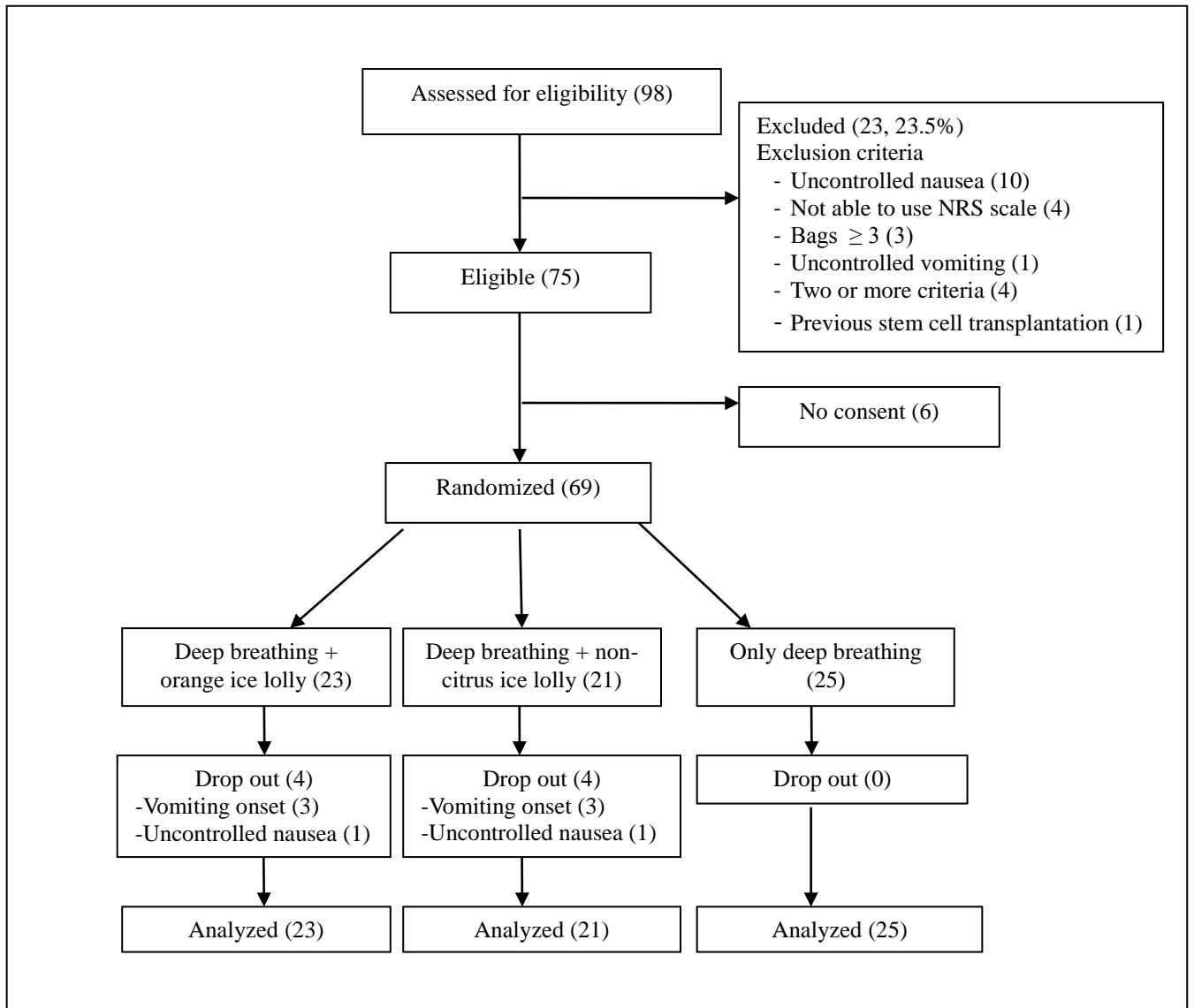
	DURING REINFUSION				IN THE FOLLOWING 48 HOURS			
	Ice lolly		Only breathing (n = 25) (n/%)	P value <sup>a</sup>	Ice lolly		Only breathing (n = 25) (n/%)	P value <sup>a</sup>
	Orange (n = 23) (n/%)	Non-citrus (n = 21) (n/%)			Orange (n = 23) (n/%)	Non-citrus (n = 21) (n/%)		
a. Controlled nausea or vomiting	21 (91.3)	20 (95.2)	23(92)	1.000	22 (95.7)	20 (95.2)	20 (80)	0.090
b. No nausea or vomiting	18 (78.3)	18 (85.7)	22 (88)	0.734	21 (91.3)	18 (85.7)	13 (52)	0.002
c. Anti-emetic rescue therapy	-	-	3 (12)	0.044	5 (21.7)	6 (28.6)	12 (48)	0.092
d. Complete protection	17 (74)	14 (70) <sup>c</sup>	16 (66.7) <sup>d</sup>	0.776	17 (73.9)	16 (76.2)	9 (36)	0.003
e. Total control	16 (69.6)	12 (60) <sup>c</sup>	13 (54.2) <sup>d</sup>	0.489	12 (52.2)	13 (61.9)	6 (24)	0.017
f. Time from infusion of stem cells to first emesis <sup>b</sup>	-	-	-	-	0-24 h 2 (8.7)	0-24 h 2 (9.5)	0-24 h 9 (35)	0.010

<sup>a</sup> Ice lolly vs. Breathing

<sup>b</sup> Calculated on the number of cases not events

<sup>c</sup> 20 patients

<sup>d</sup> 24 patients



**Figure 1** Screening, enrolment and randomization