



Original Article

Impact of Educational Interventions on Psychological Distress During Allogeneic Hematopoietic Stem Cell Transplantation: A Randomised Study.

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Competing interests: The authors declare no conflict of Interest.

Abstract. Background. Physical and psychological factors, like wrong attitudes and behaviours, can negatively influence the health outcomes of the patients receiving allogeneic hematopoietic stem cell transplantation (AHSCT). Educational interventions aiming to improve knowledge on side effects, risks, complications and preventive behaviour can reduce psychological distress, and improve quality of life (QoL). We aimed to compare a standard approach with therapeutic patient education (TPE) to analyse the impact on AHSCT patients' QoL, psychological distress and knowledge of AHSCT side effects, risks complications and preventive behaviour.

Material and methods. A prospective interventional study was conducted analysing data of 36 patients who received one of two different educational approaches, which were a standard approach (not-exposed) or TPE (exposed).

Results. In the exposed group QoL improved 14 days after transplantation (42.2 vs 25.6; $p < 0.03$) and at time of discharge (36.6 vs 54.4; $p < 0.005$). Anxiety and depression were better controlled in the exposed group, both at hospitalisation and discharge (anxiety: 48.1 vs 53.2; 46.4 vs 51.6. $p < 0.04$; depression: 49 vs 55.3; 48 vs 54.3, $p < 0.03$). Knowledge of AHSCT risks and complications improved in exposed patients, both at admission (10.1/15 vs 8/15 correct answers; $p < 0.01$) and discharge (10.7/15 vs 8.8/15 correct answer; $p < 0.03$).

Conclusions. The TPE for AHSCT patients improved knowledge, reduced anxiety and depression, which consequently increasing QoL. Therefore, we recommend our approach to further engage patients in the treatment plan, which should specifically take place prior to AHSCT initiation.

Keywords: Therapeutic patient education; Allogeneic hematopoietic stem cell transplantation; Quality of life; Psychological support; Patient engagement.

Citation: Cioce M., Lohmeyer F.M., Moroni R., Magini M., Giralardi A., Garau P., Gifuni M.C., Savoia V., Celli D., Botti S., Gargiulo G., Bonifazi F., Ciceri F., Serra I., Zega M., Sica S., Bacigalupo A., De Stefano V., Moscato U. Impact of educational interventions on

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Introduction. Allogeneic hematopoietic stem cell transplantation (AHSCT) is the standard of care for several haematological disorders.¹ AHSCT patients require hospitalisation in protected environments where they follow appropriate antimicrobial prophylaxis and prevention programs to overcome the toxic effects of the therapy minimising associated risks. However, non-relapse mortality at two years ranges between 15% and 40%, and it depends on the patients' age, comorbidities, disease, status at transplant, conditioning regimen and donor type.² Survival at two years ranges between 50% and 80%.³

AHSCT is associated with health problems occurring in the immediate post-transplant period including infections, bleeding, mucositis, fever, nausea, hypotension and shock, skin rash, acute or chronic pain and diarrhea⁴ which can negatively affect patients' QoL and survival.⁵

In addition, patients undergoing an AHSCT can present relevant psychological distress—most common depression, anxiety and sleeping problems—they might confront with primitive defence mechanisms such as denial, and projection.⁶ Depression is the most common manifestation of psychological distress in patients with neoplastic disease,⁷⁻⁹ which is even more frequent in patients with advanced disease.¹⁰⁻¹²

AHSCT requires that patients and their families change their daily life. Patients and their caregivers can reinforce their knowledge on necessary lifestyle changes following specific therapeutic, educational interventions, increasing patient engagement, collaboration with healthcare-worker, knowledge of the disease and treatment, and QoL, which can positively impact their health outcomes.^{13,14}

The use of audio-video and information material for individual learning accompanied by verbal instructions, complemented by multidisciplinary and interactive educational teaching tools notably improved knowledge and practical skills.¹⁵ Currently, no studies exist in the literature, which systematically assessed the relationship between therapeutic education and health outcomes in AHSCT.

This study aimed to compare a standard with therapeutic patient education (TPE) analysing the impact on QoL, psychological distress and knowledge of AHSCT side effects, risk factors, complications as well as preventive behaviour.

Materials and Methods.

Study design. This is an interventional, randomised (computer-generated, 1:1), double-blind study with two groups:

- *Not-exposed group.* Standard approach, printed informative material about the transplant procedure, complications, self-care, general advice, diet and safety issues, was delivered at the time of hospitalisation by the primary nurse;
- *Exposed group.* TPE conducted by a nurse, a dietician and a psychologist.

Patients have been randomised in the two groups immediately after signing written informed consent.

The study was approved by the local ethics committee on January 18, 2018 (Prot. 46787/17 – 1143/18, ID: 1767).

Inclusion/exclusion. Thirty-six patients undergoing AHSCT at our hospital (central Italy) were involved in the study from May to December 2018, of them the half came from other centres of Italy. All participants were adults (over 18 years) of both sexes and able to provide written informed consent. Exclusion criteria were the following: patient uncooperative and/or affected by mental disease, pregnant or breastfeeding women.

Sample size calculation. The sample size was calculated considering a mixed model ANOVA with repeated measures, with $\alpha=0.01$ and power 80%, $\delta=0.6325$ on two groups; and variance between groups=0.0200 and a variance "between-within groups" =0.05 for two or more repeated measures with a correlation index $\rho=0.9$. Considering a possible drop-out, we recruited 36 patients (18 patients in each group).

Therapeutic patient education. The TPE, based on a WHO working group report¹⁶, taking place about a week before transplant hospitalisation, including an interview of about 60 minutes in which the patient and the caregiver participated and verbal instructions were provided on the following areas:

- **Nursing care.** During the meeting, nurses addressed detailed AHSCT side effects, risks, complications and preventive behaviour responding on arising questions; a video of about 10 minutes was projected explaining main complications, hand hygiene, protective isolation and lower microbial load rooms (video surveillance, health call etc.). Additionally,

printed informative material (mucositis, hand hygiene, access mode, recommendations and prohibitions, multi-resistant germ brochures as well as an allogeneic transplant guide) was handed out and explained.

- Psychological. Most frequent psychological problems (anxiety and depression) in the onco-haematological area and possible interventions were addressed; a psycho-oncologist with several years of experience answered raised questions.
- Nutritional. Educational intervention according to guidelines of the International Agency for Research on Cancer (IARC) and the European Society for Clinical Nutrition and Metabolism (ESPEN) for cancer patients. Data collected in the nutritional education area evaluating caloric-proteic malnutrition in patients undergoing AHSCT is not part of this publication.

Outcome measures. The 36 patients observed were evaluated for QoL with the Cancer Linear Analogue Scale (CLAS) at time of admission (T0), day of the AHSCT (T1), 7 and 14 days after the AHSCT (T2/T3) as well as at discharge (T4). CLAS investigates energy level, ability to perform daily activities and overall QoL.

The Symptom Checklist-90-R (SCL-90-R) was performed at T0 and T4, assessing symptom severity of psychological distress in the week before checklist performance. The patient's responses are interpreted based on nine primary symptomatological dimensions (cut-off \geq 55).

The degree of knowledge regarding concepts addressed during the TPE was assessed through a structured multiple-choice questionnaire at T0 and T4, which was composed of 15 items, 5 for each profession involved. The reliability of the internal consistency has been tested through the alpha Cronbach and the validity of the content through the Content Validity Index¹⁷. The internal consistency of the instrument used, measured by calculating the alpha of Cronbach, was 0.83.

Statistical analysis. The sample was described in its socio-demographic and clinical characteristics through descriptive statistic techniques. Qualitative variables have been described using absolute frequencies and percentages, while quantitative variables have been summarised through the range, mean, median and standard deviation. Normality of data was verified with the Shapiro-Wilk test. Comparisons were performed with t-tests for paired data or Kruskal-Wallis, for nonparametric variables. Mixed model ANOVA and generalised linear model, where the between-subjects factor was represented by two groups (exposed and not-exposed) and the within-subjects factor is represented by the time was used for repeated measurements.¹⁸ Bonferroni correction was applied. Data have been stored and managed in spreadsheet (Data set created on

a Microsoft Excel 2016 spreadsheet for Mac Vers. 2016/14.5.5). Statistical analyses were carried out with Stata7IC software[14.2 for Mac (64-bit Intel), Vers. January 09 2017, 800-STATA PC-Lakeway]. Statistical significance was set at $p < 0.05$.

Results. Of 36 patients included in the study, 18 have been randomised to the not-exposed group (50.0%), with 40% (7/18) coming from other centres, and 18 have been randomised to the exposed group (50.0%), with 60% (11/18) from other centres. The proportion of missing data at the end of the study was minimal (<5%). The sample consisted mainly of male patients ($n=22$, 61.1%), most of them in the not-exposed group (83.3% of males in the group) while 61.1% of patients in the exposed group were females, $p=0.006$. **Table 1** describes the clinical and demographic characteristics of the cohort.

Table 2 demonstrates the results regarding QoL assessed with CLAS. The exposed group had statistically significant ($p=0.03$) better scores 42.2 versus 25.6 (not-exposed group) at T3 (14 days after AHSCT) when questioned about their general QoL. The difference between the two groups was more significant at discharge: 36.6 (exposed) and 54.4 (not exposed), $p=0.05$.

Regarding psychological distress assessed with SCL-90-R, statistically significant results have been highlighted in the area of interpersonal hypersensitivity (I-S) where the main effect of group's p -value was 0.04. More detailed, in the not-exposed group, the mean discomfort related to T0 was 47.9 (± 11.1) and was 43.7 (± 5.7) in T4. In the exposed group, the mean discomfort was 43.1 (± 4.9) and was 41.3 (± 1.9) in T4. For the areas anxiety (ANX) and depression (DEP), all patients, exposed and not-exposed had symptoms at T0 and T4, whose intensity did not deviate from the average values found in the reference sample. The anxiety score (ANX) decreased from 53.2 to 51.6 in not-exposed patients and from 48.1 to 46.4 in exposed patients (groups main effect $p=0.03$). The DEP score increased from 55.3 to 54.2 in not-exposed patients and decreased from 49 to 48 in exposed patients (groups main effect $p=0.03$). Although the p -value was not significant, it is important to underline that, in the area of paranoid ideation (PAR), no elements of discomfort are highlighted at both T0 and T4; the score decreased from 44.1 to 42.1 in not-exposed patients and from 42.4 to 40 in exposed patients (**Table 3**).

Table 4 shows the results of the 15-item questionnaire about knowledge acquisition in the three areas (nursing care, psychological and nutritional). Both total scores at T0 and T4 were statistically significant, demonstrating increased awareness in the exposed group compared with the not-exposed group. More detailed, the correct answers given, at T0 in the exposed group were 10.1/15 compared with 8/15 in the not-

Table 1. General characteristics.

	Not Exposed (N=18)		Exposed (N=18)		p-value
	n	%	n	%	
GENDER					0.006
	<i>Female</i>	3	16.7	11	61.1
	<i>Male</i>	15	83.3	7	38.9
AGE					0.866
	<i>21-30</i>	1	5.6	1	5.6
	<i>31-40</i>	2	11.1	3	16.7
	<i>41-50</i>	1	5.6	1	5.6
	<i>51-60</i>	7	38.9	9	50.0
	<i>61-70</i>	7	38.9	4	22.2
DISEASE					0.621
	<i>AML</i>	6	33.3	6	33.3
	<i>MM/PCD</i>	0	0	1	5.6
	<i>CLL</i>	2	11.1	0	0.0
	<i>ALL</i>	5	27.8	4	22.2
	<i>Ly</i>	1	5.6	1	5.6
	<i>MDS/MPS</i>	4	22.2	6	33.3
HSE SOURCE					0.416
	<i>BM</i>	10	55.6	7	38.9
	<i>PBSC</i>	8	44.4	10	55.6
	<i>CB</i>	0	0	1	5.6
TRANSPLANTATION					0.594
	<i>HLA Id. Sib.</i>	4	22.2	5	27.8
	<i>Unrelated Donor</i>	4	22.2	6	33.3
	<i>Fam. Mismatch /Aplo</i>	10	55.6	7	38.9
	<i>Fam. Match</i>	0	0	0	0
CONDITIONING					0.388
	<i>TBF</i>	14	77.8	16	88.9
	<i>CFM</i>	2	11.1	0	0
	<i>BF</i>	0	0	1	5.6
	<i>F</i>	1	5.6	1	5.6
	<i>CF</i>	1	5.6	0	0
TBY					0.482
	<i>No</i>	15	83.3	17	94.4
	<i>Yes, 12 Gy</i>	2	11.1	1	5.6
	<i>Yes, 2 Gy</i>	1	5.6	0	0
COMPLICATIONS					0.348
	<i>No</i>	13	72.2	16	88.9
	<i>aGvHD</i>	4	22.2	1	5.6
	<i>Haemorrhagic cystitis</i>	1	5.6	1	5.6
	<i>Pneumonia</i>	0	0	0	0
	<i>VOD</i>	0	0	0	0

AML: Acute Myeloid Leukemia; MM/PCD: Multiple Myeloma/ Plasma Cells Diseases; CLL: Chronic Lymphocytic Leukemia; ALL: Acute Lymphocytic Leukemia; Ly: Lymphoma; MDS/MPD: Myelodysplastic Syndromes / Myeloproliferative Diseases; BM: Bone Marrow; PBSC: Peripheral Blood Stem Cell; CB: Cord Blood; HLA: Human Leukocyte Antigen; TBF: Thiotepa Busulfan Fludarabine; CFM: Cyclophosphamide Melphalan Fludarabine; BF: Busulfan Fludarabine; F: Fludarabine; CF: Cyclophosphamide Fludarabine; TBY: Total Body Irradiation; aGvHD: Acute Graft versus Host Disease; VOD: Veno Occlusive Disease. Statistical test performed χ^2 test of Fisher's Exact Test, when appropriate.

Table 2. Quality of life results using CLAS

	Not exposed		Exposed		p-value
	mean	SD	mean	SD	
ENERGY					
T0	74.7	18.2	65.3	22.0	0.22
T1	55.2	24.7	44.7	18.7	0.15
T2	40.6	22.0	38.9	26.5	0.61
T3	32.2	16.3	41.4	20.8	0.27
T4	39.9	18.7	56.9	26.1	0.08
ABILITY TO CARRY OUT DAILY LIFE ACTIVITIES					
T0	74.2	21.0	68.9	21.0	0.51
T1	55.7	27.2	43.1	17.2	0.08
T2	40.3	26.8	38.6	24.4	0.72
T3	30.6	16.3	42.2	21.0	0.16
T4	37.3	24.7	54.2	26.2	0.08
OVERALL QUALITY OF LIFE					
T0	68.4	25.5	70.3	20.4	0.88
T1	39.2	27.2	41.4	19.6	0.75
T2	33.7	27.2	40.0	24.4	0.60
T3	25.6	20.0	42.2	23.8	0.03
T4	36.6	24.6	54.4	26.5	0.05

T0: admission; T1: hematopoietic stem cell transplantation (HSCT); T2: +7 day after HSCT; T3: +14 day after HSCT; T4: discharge.

Table 3. Psychological distress evaluation with SCL-90-R.

	Not-exposed		Exposed		p-value*
	T0	T4	T0	T4	
	mean ± SD	mean ± SD	mean ± SD	mean ± SD	
SOM	53.1 ± 13.0	56.4±11.5	50.2±12.2	51.2±7.6	0.11
O-C	47.6 ± 10.5	47.2±11.4	46.1±9.5	45.9±8.1	0.48
I-S	47.9 ± 11.1	43.7±5.7	43.1±4.9	41.3±1.9	0.04
DEP	55.3 ± 13.9	54.2±10.0	49.0±9.6	48.0±5.8	0.03
ANX	53.2 ± 11.7	51.6±11.5	48.1±8.6	46.4±9.4	0.03
HOS	47.3 ± 9.4	46.4±8.0	45.4±8.7	42.9±4.0	0.15
PHOB	51.0 ± 9.5	52.6±10.5	50.6±9.7	47.3±5.1	0.36
PAR	44.1 ± 9.5	42.1±5.5	42.4±5.2	40.0±3.6	0.30
PSY	51.5 ± 10.1	50.2±10.1	48.1±6.0	45.4±4.4	0.09
Sleep	49.6 ± 10.4	51.9±14.2	47.6±8.9	52.3±12.1	0.66
GSI	50.7 ± 13.0	50.7±10.6	46.3±9.2	45.4±6.3	0.07
PST	49.4 ± 12.7	48.9±10.0	46.3±10.7	44.4±6.8	0.13
PSDI	52.6 ± 10.3	55.0±11.2	47.4±9.7	50.4±9.0	0.06

T0: admission; T4: discharge; SOM: Somatisation; O-C: Obsessive-Compulsive; I-S: Interpersonal Sensitivity; DEP: Depression; ANX: Anxiety; HOS: Hostility; PHOB: Phobic Anxiety; PAR: Paranoid Ideation; PSY: Psychoticism; GSI: Global Severity Index; PST: Positive Symptom Total; PSDI: Positive Symptom Distress Index.

*The p-value in the table is related to the main effect of group in a two-way mixed model ANOVA where TIME is the within-subjects factor and GROUPS (exposed/not exposed) is the between subjects factor.

exposed group ($p < 0.0$); instead, at T4, results were 10.7/15 in the exposed group compared with 8.8/15 in the not-exposed group ($p < 0.03$).

Discussion. Our data demonstrate that the TPE, taking place about a week before transplant hospitalisation,

statistically significant improved patients' knowledge of AHSCT side effects, risks, complications as well as preventive behaviour. Further, we demonstrated that knowledge gain reduced psychological distress, improving QoL in our cohort.

More detailed, we noted statistically significantly

Table 4. Knowledge acquisition about AHSCT side effects, risks, complications and preventive behaviour measured with a validated 15-item questionnaire.

	Not-exposed		Exposed		p-value
	mean	SD	mean	SD	
Nursing care area T0	1.6	1.0	2.7	0.9	0.01
Nursing care area T4	2.9	0.9	3.0	1.2	0.88
Nutritional area T0	2.9	0.8	3.5	0.9	0.05
Nutritional area T4	3.0	1.0	3.7	0.8	0.03
Psychological area T0	3.7	1.3	3.9	0.8	0.76
Psychological area T4	3.1	1.3	4.1	0.9	0.01
Total T0	8.0	2.1	10.1	1.5	0.00
Total T4	8.8	2.2	10.7	2.2	0.03

T0: admission; T4: discharge.

increased knowledge in the total scores of the exposed group compared with the not-exposed group, both at T0 ($p=0.0$) and T4 ($p=0.3$). We based the development of our TPE on findings by Friedman et al. (2011)¹⁹ who reinforced the thesis that teaching strategies using audio-video presentations, verbal instructions and personalised information material, assuring an appropriate level for independent study, are more effective than traditional methods to improving knowledge and behaviour of patients. Bennet et al. (2016)²⁰ evaluated educational strategies in adult cancer patients, in a systematic review of 14 randomised clinical trials, which showed that the integration of different educational modalities is effective to reduce fatigue and anxiety improving overall QoL.

Furthermore, we noted that the nursing care score at T0 was statistically significant ($p=0.01$) whereas at T4 not ($p=0.88$); this might be explainable with the intense training and information the exposed group received during the TPE by nurses. To improve our approach further, we suggest repeating parts of the teaching during hospital admission to ensure that preventive behaviour and attitudes will be remembered.

Likewise, we noticed that psychological distress was significantly improved at T4 ($p=0.01$), but not at T0 ($p=0.76$). This result can be explained that the intervention of different health workers, during the TPE, reduces uncertainties of the transplantation path, which positively impacts the patient's psychological state.

Our conclusions can be further confirmed with data on psychological distress assessed with SCL-90-R. We showed significant differences between the two groups in the areas ANX and DEP. Patients of the exposed group, compared to the not-exposed group, showed that they went through the therapeutic journey with a lower level of fear, worry and demoralisation. The TPE allows the patient an adequate containment of potential distress such as fear, worrying and sadness, making the state of anxiety and depression not requiring specialist psychotherapeutic and psychiatric interventions. This result has been obtained through description, explication and instruction of the possible risks associated with

admission to a lower microbial load room and possible side effects of AHSCT treatment. These data are in accordance with the results by Fawzy et al. (1993)²¹ who demonstrated that the intervention of a 6-week psychotherapeutic group—including educational interventions as psychological support, stress management and development of coping skill—was associated with lower mortality in patients with malignant melanoma after six years follow-up. Donker et al. (2019)²² evidenced that psychological education (information, teaching material and advice) reduced levels of psychological distress and specifically depression.

Related to reduced psychological distress, before and during AHSCT, is the improvement of QoL. Data collected show that the TPE for patients and their caregivers reduced psychological distress and improved statistically significant QoL ($p=0.03$) at T3 assessed with CLAS. Several studies confirm that educational interventions improve knowledge of AHSCT and QoL in the long term.²³ Kirsch et al. (2012)²⁴ demonstrated the effectiveness of educational/therapeutic interventions, which acted synergistically, on the strengthening of problem-solving during treatment and follow-up. Instead, Marques et al. (2012)²⁵ showed that QoL, measured with QLQ-C30, has lower average scores in the pancytopenia compared to the pre-transplant phase. This is probably due to the critical moments of treatment when complications can occur, endangering patients lives or interfering negatively with their QoL. Accordingly, we recorded lower average values, which were even lower in the exposed group, both at T3 and T4. After hospitalisation, a progressive improvement to perform daily activities and QoL, equal if not better than in the pre-transplant phase, is usually expected between 9 to 12 months, even if a percentage of patients suffering from late complications, such as chronic Graft-versus-Host Disease (GvHD), reach the pre-transplant level.²⁶

Limitations. Among our limitations is the relatively small, but notwithstanding adequate sample size.

According to our protocol, patients were randomly assigned and which led to more women in the exposed group. Furthermore, data is not generalisable to other contexts. Therefore, our study necessitates confirmation on a larger cohort and replication in different settings always in the context of AHSCT.

We do not know if the point in time providing the two different approaches might have influenced our results; exposed patients had one-week time in their familiar surroundings to process the received information after they participated on the TPE compared with the not-exposed group, which received printed material at the time of hospitalisation. This aspect was not investigated in our study.

Conclusions. In conclusion, therapeutic education is a relevant aspect of clinical pathways. Although several studies describe its usefulness in some areas, evidence to support its effectiveness in AHSCT is lacking. Obtaining information through educational interventions is a fundamental right for patients

undergoing AHSCT. We hope this approach will spread widely as an educational methodology structured in a multidisciplinary development perspective of real patient care and its centrality in the care processes. The results of this study show that a TPE before AHSCT improved knowledge on AHSCT side effects, risks, complications and preventive behaviour, which reduced in our cohort anxiety and depression positively affecting QoL. Based on our data, we recommend engaging patients in AHSCT treatment as much and as early as possible, allowing an active role in decision-making processes, which improves adequate self-care. Furthermore, we believe that it might be positive if the AHSCT topics addressed before hospitalisation are repeated during admission, based on individual needs and capacities.

The effectiveness of TPE in AHSCT should be confirmed in future multicentre study in the GITMO group (Gruppo Italiano per il Trapianto di Midollo Osseo, cellule staminali emopoietiche e terapia cellulare).

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