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Nutritional intervention with TGF-beta enriched food for special medical purposes (TGF-FSMP) is associated with a reduction of malnutrition, acute GVHD, pneumonia and may improve overall survival in patients undergoing allogeneic hematopoietic stem transplantation

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ABSTRACT

Malnutrition in allogeneic stem cell transplant (allo-SCT) is associated with poor outcomes. Supplementation with Foods for Special Medical Purposes may be a valid alternative to enteral nutrition or total parental nutrition to reduce malnutrition in allo-SCT. In this study, 133 patients consecutively allo-transplanted were assessed for nutritional status by Patient- Generated Subjective Global Assessment (PG-SGA) and supplemented with TGF-beta enriched Food for Special Medical Purposes (TGF-FSMP).

PG-SGA, gold standard for nutritional assessment in oncologic patients, was assessed at admission and on day 0, +7, +14, +21, and + 28 from transplant and categorized as follows: A = good nutritional status; B = moderate malnutrition; C = severe malnutrition. TGF-FSMP (Modulen-IBD) is currently used in Inflammatory Bowel Diseases (IBD) as primary nutritional support and in this study the dose was calculated according to BMI and total daily energy expenditure (TDEE). The patients assuming ≥50% of the prescribed TGF-FSMP dose were classified in Group A; the patients who received < 50% were included in Group B per protocol. The primary endpoint of the study was the assessment of the malnourished patients in Group A and B at day+28 after transplantation, according to the criteria of PG-SGA C categorization. At day +28 after transplant: i) patients in Group A were significantly less severely malnourished than patients in the Group B (21/76,28% vs 42/53, 79% respectively, OR 2.86 - CI 1.94–4.23 -, $p = 0.000$); ii) the incidence of severe (MAGIC II-IV) aGVHD and of any grade gastrointestinal (GI) aGVHD was higher in Group B than in Group A, (43% vs 21% $p = 0.003$) and (34.5% vs 9.2% $p = 0.001$); iii) Pneumonia was more frequent in the malnourished patients of Group B than in well/moderate nourished patients of Group A (52.7% vs 27.6% $p = 0.002$). In group A parenteral nutrition was avoided more frequently than in group B (67.5% vs 33.3% $p = 0.000$) and a median hospital stay of 27 days in comparison to 32 was reported ($p = 0.006$). The estimated median overall survival (OS) of the population was 33 months in Group A and 25.1 months in group B ($p = 0.03$). By multivariate and ANN analysis, TGF-FSMP TR < 50% assumption was significantly correlated with malnutrition, severe and GI aGVHD, pneumonia and reduced OS.

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Table 1
Clinical characteristics of enrolled patients.

	Study Cohort	Extended Cohort	P. value	Cumulative Cohort
Total	51	82	NS	133
Sex *(F/M)*	22/29	26/56	NS	48/85
Age *(Median)*	55 (range 20–72)	56 (range 17–78)	NS	56 (range 17–78)
Median follow-up *(months)*	11 (range 1–41)	12 (range 1–59)	NS	12 (range 1–59)
Diagnosis *(AL-MDS-MPD* vs *LPD* vs *I)*	39/12/0 (76.5%/23.5%)	58/21/3 (70.7%/25.6%/3.7%)	NS	97/33/3 (72.9%/24.8%/2.3%)
Disease status at admission *(CR/MRD/AD)*	17/26/8 (33.3%/51%/15.7%)	25/43/14 (30.5%/52.4%/17.1%)	NS	42/69/22 (31.6%/51.9%/16.5%)
Donor type *(MRD/MUD/Haplo)*	21/20/10 (41.2%/39.2%/19.6%)	15/43/24 (18.3%/52.4%/29.3%)	0.015	36/63/34 (27.1%/47.4%/25.5%)
Stem cell source *(PB/BM)*	48/3 (94.1%/5.9%)	74/8 (90.2%/9.8%)	NS	122/11 (91.7%/8.3%)
Conditioning (MA/RIC)	32/19 (62.7%/37.3%)	46/36 (56.1%/43.9%)	NS	78/55 (58.6%/41.4%)
Nutritional status at admission following PG-SGA *(Score A/B/C)*	38A / 12B / 1C (74.5%/23.5%/2%)	57A / 22B / 1C (71.2%/27.5%/1.3%)	NS	95A / 34B / 2C (72.5%/26%/1.5%)

F = female, M = male, AL = Acute Leukemia, MDS = Myelodysplastic Syndrome, MPD = Myeloproliferative Disease, LPD = Lymphoproliferative Disease, I = Immunodeficiency, CR = Complete Remission, MRD = Minimal Residual Disease, AD = Advanced Disease, MRD = Matched Related Donor, MUD = Matched Unrelated Donor, Haplo = Haploidentical Related Donor, PB = Peripheral Blood, BM = Bone Marrow, MA = Myeloablative Conditioning, RIC = Reduced Intensity Conditioning, PG-SGA = Patient- Generated Subjective Global Assessment.

1. Introduction

Malnutrition is associated with poor outcomes in treated cancer patients [1], also in the case of patients submitted to allogeneic hematopoietic stem cell transplantation (allo-SCT) [2]. In the setting of allo-SCT malnutrition-derived immune-system dysfunction could lead to increased risk of infection or Graft Versus Host Disease (GVHD) [2]. To correct malnutrition several options are available: firstly patients are encouraged to consume regular meals during hospitalization and in addition to food, macro- and micro-nutrients integration is warranted [2]. Artificial nutrition could be divided into Enteral nutrition (EN) and parenteral nutrition (PN). EN is considered the optimal option to ensure adequate intake of proteins and calories [3]. Although enteral nutrition through a nasogastric tube is recommended [4], its placement is not widely accepted, especially in the setting of allo-SCT [5]. Thus, the use of Foods for Special Medical Purposes (FSMPs) [6] can be considered an alternative nutritional supportive approach for transplanted patients to avoid malnutrition. FSMPs are a group of artificial foods able to ensure a complete nutritional support even if taken exclusively. Several options are available for oncologic patients, but there are no data about their use after allo-SCT.

TGF-beta enriched FSMP (Modulen-IBD) is approved for nutritional supplementation in patients with inflammatory bowel disease (IBD) [7] and due to its biological properties it has been successfully tested in our previous study in patients who underwent allo-SCT [8]. Potential benefits of TGF-FSMP assumption were observed not only in malnutrition reduction but also in acute gastrointestinal GVHD prevention [8].

In the previous study [8], 51 patients were supported with TGF-FSMP to correct malnutrition evaluated according to the Patient-Generated Subjective Global Assessment (PG-SGA) questionnaire, a standard tool for nutritional monitoring and triaging for nutritional interventions in patients with cancer [9,10]. In this study, patients assuming more than or equal to 50% of the prescribed dose were classified as adequately treated according to study protocol: these patients reported less severe malnutrition (13% vs 88.9%, $p = 0.000$) and a reduced incidence of any grade acute gastrointestinal GVHD (0% vs 38%, $p = 0.006$). After this study, further 82 consecutive patients have been prospectively treated with TFG-FSMP. Thus, a comprehensive analysis on 133 consecutive patients treated with TGF-FSMP was conducted to confirm the results of our pivotal study [8] on a larger population and to identify the features associated with better outcomes.

2. Patients and methods

One hundred and thirty-three patients consecutively allotransplanted between April 2018 and February 2023 were assessed for nutritional status by PG-SGA and supplemented with TGF-FSMP according to the rules of the previous pilot study [8].

The clinical characteristics of the 133 patients are reported in Table 1. The two cohorts were comparable for demographic, clinical, hematological and transplant characteristics, except for donor type ($p = 0.015$): in the extended cohort more patients had a matched-unrelated or haploidentical donor. GVHD prophylaxis consisted in Cyclosporine, Methotrexate and ATG (Anti-Thymocyte Globulin, Grafalon) for matched-related and unrelated donors, and in sirolimus, mycophenolate mofetil and post-transplant cyclophosphamide for haploidentical donors.

PG-SGA was assessed at admission and on day 0, +7, +14, +21, and + 28 from transplant (day 0 was the transplant day) [8]. As known, PG-SGA is composed of an objective section and of a patient-reported section. The first section reports the overall nutritional status, and it is indicated with an alphabetical score according to anthropometric measures and history (A = good nutritional status; B = moderate malnutrition; C = severe malnutrition). The second one is a numeric score that is calculated using four items self-reported by patients (weight loss, food intake, symptoms with a nutritional impact, and physical activity) [9,10].

On admission, most of the patients had good nutritional status in both cohorts, with no statistical difference. TGF-FSMP was proposed to all the patients since admission to the department. Treatment plan was carried out as previously described [8]: briefly, the dose was calculated according to BMI and total daily energy expenditure (TDEE). The impact of malnutrition on other clinical outcomes was explored in relation to TGF-FSMP intake, defined as the percentage of the prescribed dose (treatment ratio—TR). As reported in the pilot study [8], no minimal dose was defined as clinically effective. The patients assuming more or equal than 50% of the prescribed TGF-FSMP (corresponding to a Treatment Ratio - TR - $\geq$ 50%) were considered to have received an "adequate" dose of supplementation and have been classified in Group A; the patients who did not take a sufficient dose of TGF-FSMP, corresponding to a Treatment Ratio (TR) < 50% of the prescribed dose, were classified in Group B.

In patients refusing TGF-FSMP, parenteral nutrition (PN) was administered to ensure adequate calories and protein intake [4], according to EBMT Handbook criteria. Parenteral nutrition was classified according to its duration: PN, defined as support for EN, or Total Parenteral Nutrition (TPN) defined as >7 days of exclusive parenteral nutritional support. As previously reported [8], GVHD was defined according to MAGIC criteria [11], nutritional status on day +28 after transplantation was considered the primary endpoint [8] and the well and moderate nourished patients with PG-SGA A and PG-SGA B, respectively, were grouped together to be compared with severe malnourished patients (PG-SGA C). Hospital stay was calculated from transplantation day until to discharge to normalize data.

Table 2
Group A (≥TR 50%) and Group B (< TR 50%) distribution according to TGF-FSMP assumption in all cohorts.

	Study Cohort			Extended Cohort			Cumulative Cohort		
	GROUP A*	GROUP B*	P. value	GROUP A*	GROUP B*	P. value	GROUP A*	GROUP B*	P. value
Total	24/51 (47%)	27/51 (53%)	/	52/80 (65%)	28/80 (35%)	/	76/131 (58%)	55/131 (42%)	/
Sex *(F/M)*	9/15	13/14	NS	18/34	7/21	NS	27/49	20/35	NS
Age *(Median)*	54	54	NS	56	56,5	NS	55	56	NS
Median follow-up *(months)*	12.5	10	NS	10	14	NS	12.5	13.2	NS
Diagnosis *(AL-MDS-MPD* vs *LPD* vs *I)*	18/6/0	21/6/0	NS	39/11/2	17/10/1	NS	57/17/2	38/16/1	NS
Disease status at admission *(CR/MRD/AD)*	6/13/5	11/13/3	NS	16/27/9	9/15/4	NS	22/40/14	20/28/7	NS
Donor type *(MRD/MUD/Haplo)*	10/11/3	11/9/7	NS	11/28/13	2/15/11	NS	21/39/16	13/24/18	NS
Stem cell source *(PB/BM)*	22/2	26/1	NS	46/6	26/2	NS	68/8	52/3	NS
Conditioning (MA/RIC)	14/10	18/9	NS	30/22	14/14	NS	44/32	32/23	NS
Nutritional status at admission following PG-SGA *(Score A/B/C)*	19A/5B/0C	19A/7B/1C	NS	38A/14B/0C	19A/8B/1C	NS	57A/19B/0C	38A/15B/2C	NS

F = female, M = male, AL = Acute Leukemia, MDS = Myelodysplastic Syndrome, MPD = Myeloproliferative Disease, LPD = Lymphoproliferative Disease, I = Immunodeficiency, CR = Complete Remission, MRD = Minimal Residual Disease, AD = Advanced Disease, MRD = Matched Related Donor, MUD = Matched Unrelated Donor, Haplo = Haploidentical Related Donor, PB = Peripheral Blood, BM = Bone Marrow, MA = Myeloablative Conditioning, RIC = Reduced Intensity Conditioning, PG-SGA = Patient- Generated Subjective Global Assessment.

2.1. Statistical analysis

Correlation between variables and clinical outcomes (Overall Survival - OS -, acute GVHD, gastrointestinal acute GVHD, chronic GVHD, relapse incidence, infections such as pneumonia, sepsis, or enteritis) was studied with the Mann–Whitney or Wilcoxon test for continuous variables (Treatment Ratio, age, hospital stay), Kaplan–Meier plots for OS, incidence of acute and chronic GVHD according to the log-rank test for univariate analysis. Chi-square Fisher test for univariate analysis for categorical variables was used. In the log-rank and Fisher tests, patients were grouped according to the treatment ratio (TR) (TR ≥ or < 50% based on the study protocol, Group A and Group B, respectively).

For the multivariable analysis on OS and acute GVHD incidence at 4 months after transplantation, the cox regression model for time dependent variables was used. Artificial Neural Network analysis for principal outcomes was performed with the framework described by Caocci et al. [12] and with the specification of the study cohort as a training set. The study was conducted in compliance with current national and European legislation on clinical trials and in accordance with the Declaration of Helsinki and the principles of good extended use.

Overall, TGF-FSMP was administered to 133 consecutive transplanted patients of which 51 in the first investigational study [8] and 82, prospectively, as extended cohort. The clinical characteristics of the 133 patients are reported in Table 1.

The two cohorts were comparable for the demographic, clinical, hematological and transplant characteristics, except for donor type ($p = 0.015$): in the extended cohort most patients had a matched-unrelated or haploidentical donor. On admission most of the patients had good nutritional status in both cohorts.

3. Results

For analysis purposes, patients were grouped according to TGF-FSMP treatment ratio (TR) assumption: in Group A were included the patients who received TR ≥ 50%; in Group B were included those who had TR < 50%, as previously reported [8]. Refusal of the FSMP was principally due to nausea, dysgeusia or disgusting taste. Every patient was free do decide whether to assume FSMP or not, according to study rules and according to assumption proportion (TR) patients were divided into the two groups.

Table 3
Incidence of main complications after alloHSCT according to TGF-FSMP assumption (Group A vs- Group B), categorized according to Study Cohort, Extended use Cohort and Cumulative Cohort.

	Study Cohort			Extended use Cohort			Cumulative Cohort		
	GROUP A*	GROUP B*	P.value	GROUP A*	GROUP B*	P. value	GROUP A*	GROUP B*	P. value
Severe malnutrition @ + 28d (PG-SGA C)	3/24 (12.5%)	24/27 (88.9%)	**0.000**	18/52 (34,6%)	18/26 (69,2%)	**0.004**	21/76 (27,6%)	42/53 (79,2%)	**0.000**
Incidence of aGVHD (%)	9 (37.5%)	14 (51.9%)	NS	21 (40.4%)	16 (57.1%)	NS	30 (39.5%)	30(54.5%)	NS
Incidence of **grade II-IV aGVHD** (%)	4/24 (16.7%)	11/27 (40.7%)	0.06 (NS)	9/52 (17.3%)	12/26 (46.1%)	**0.008**	13/76 (17.1%)	23/53 (43.4%)	**0.001**
Incidence of **gastrointestinal aGVHD** (%)	1 (4.2%)	8 (29.6%)	**0.005**	6 (11.5%)	11 (39.3%)	**0.017**	7 (9.2%)	19 (34.5%)	**0.001**
Incidence of cGVHD (%)	5 (20.8%)	3 (11.1%)	NS	8 (15.4%)	9 (32.1%)	NS	13 (17.1%)	12 (21.8%)	NS
Sepsis (%)	7 (29.2%)	15 (55.6%)	NS	25 (48.1%)	15 (53.6%)	NS	32 (42.1%)	30 (54.5%)	NS
Pneumonia (%)	3 (12.5%)	13 (48.1%)	**0.006**	18 (34.6%)	16 (57.1%)	**0.035**	21 (27.6%)	29 (52.7%)	**0.002**
Enteritis (%)	4 (16.7%)	10 (37%)	NS	12 (23.1%)	6 (21.4%)	NS	16 (21.1%)	16 (29.1%)	NS
Relapse Incidence (%)	7/24 (29.1%)	7/27 (25.9%)	NS	9/52 (17.3%)	6/26 (23.1%)	NS	16/76 (21%)	13/53 (24.5%)	NS
No Parenteral nutrition	18/24 (66.6%)	6/27 (22.2%)	**0.000**	34/53 (64.1%)	12/27 (44.4%)	NS	52/77 (67.5%)	18/54 (33.3%)	**0.000**
Hospital Stay (median)	29	30	NS	27	33	**0.04**	27	32	**0.006**
Survival after alloHSCT (Median, months)	24.1	13.9	NS	37.1	29	NS	33.3	25.2	**0.003**

PG-SGA Patient Generated Subjective General Assessment; aGVHD acute Graft Versus Host Disease; cGVHD chronic Graft Versus Host Disease; Grade II-IV according to MAGIC classification.

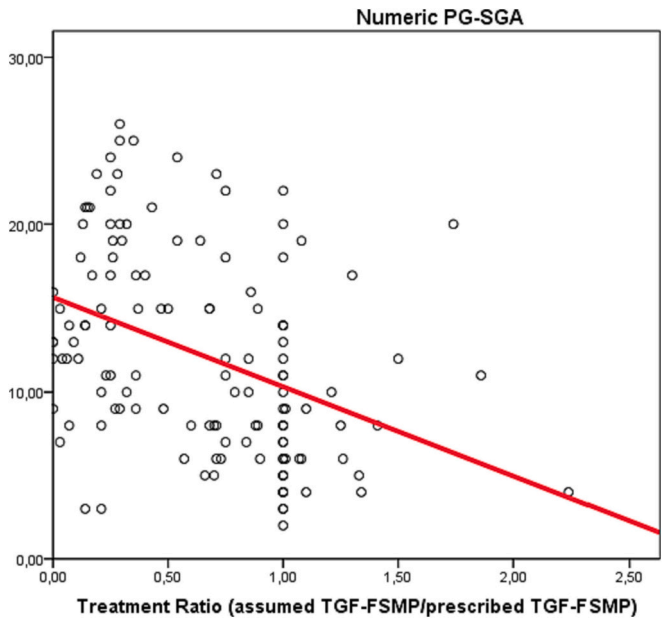

Fig. 1. Correlation between TR and PG-SGA in cumulative cohort: higher subjective values are associated with low TR (reduced assumption in relationship to prescribed dose).

No differences were found in patients' characteristics on admission for transplant between the groups (Table 2).

The primary endpoint of the study was the assessment of the malnourished patients in Group A and B 28 days after transplant, as defined according to the criteria of PG-SGA C categorization.

Group A consisted of 76 patients who had received TGF-FSMP TR ≥ 50% (mean assumption 98%), while Group B included 55 patients who assumed TGF-FSMP TR < 50% (mean assumption 21%).

On day +28 after transplant, patients in Group A were significantly less severely malnourished than patients in Group B (21/76,28% vs 42/53, 79% respectively, OR 2.86 - CI 1.94–4.23 -, $p = 0.000$) (Table 3).

A statistical inverse correlation was found between the cumulative dose of prescribed preparation and PG-SGA values registered 28 days after transplant ($R = 0.153$, $p = 0.000$ (Fig. 1)). Higher values of PG-SGA are representative of higher malnutrition symptoms burden.

The incidence of any grade of aGVHD was similar both in Group A and B (39.5% vs 54.5% $p = 0.09$). However, the incidence of severe (MAGIC II-IV) aGVHD and of any grade gastrointestinal (GI) aGVHD was higher in Group B than in Group A, (43% vs 21% $p = 0.003$) (Fig. 2) and (34.5% vs 9.2% $p = 0.001$) (Fig. 3), respectively. The mean TGF-FSMP assumption was 72.2% of the prescribed dose in patients who didn't experience GI aGVHD and 42.4% in patients with GI aGVHD ($p = 0.005$). No significant difference was found in the cumulative incidence of chronic GVHD between Group A and Group B (17.1% vs 21.8% $p = 0.49$).

Pneumonia was more frequent in patients in Group B than in Group A patients (52.7% vs 27.6% $p = 0.002$).

Concerning enteritis and sepsis there was no statistical difference between the two groups (Table 3).

The estimated median overall survival (OS) of the population was 33 months in Group A and 25.1 months in group B ($p = 0.03$), Fig. 4. The relapse incidence was 21.1% in Group A and 24.1% in Group B ($p = 0.683$).

Parenteral nutrition was avoided in 52 out of 77 patients in Group A in comparison to 18/54 in Group B ($p = 0.000$). Median hospital stay was 27 days in Group A and 32 days in Group B ($p = 0.006$).

Considering the whole population (133 patients), at the

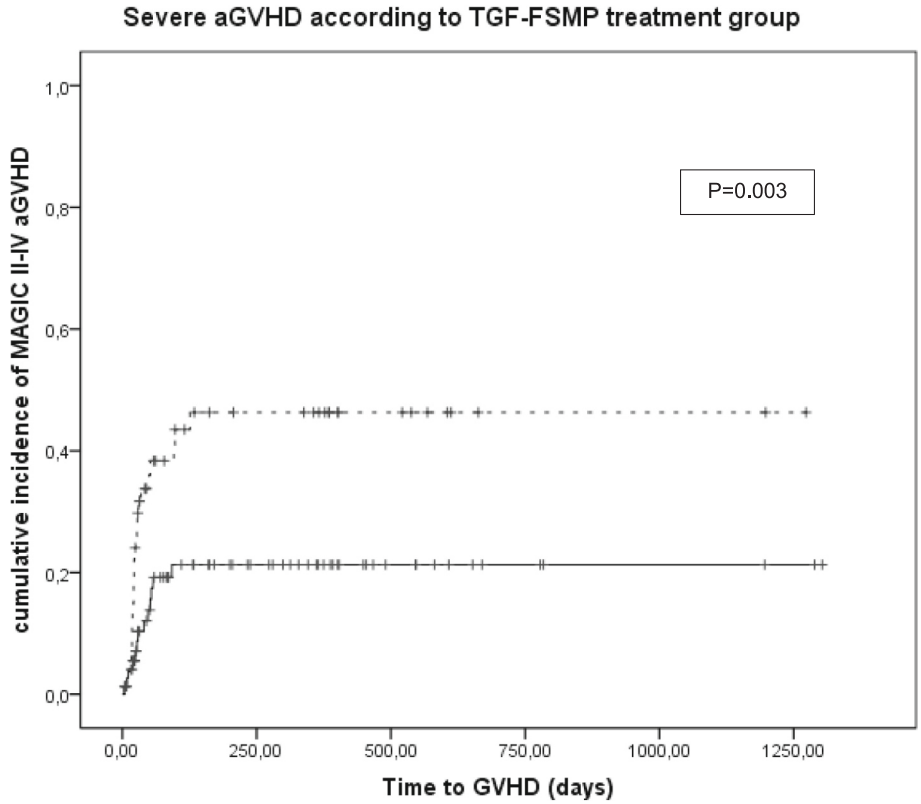

Fig. 2. Cumulative incidence of severe aGVHD (Magic II-IV) according to treatment Group:
Group A - continuous line –assumption of TGF-FSMP ≥ TR50%.
Group B – dotted line - assumption of TGF-FSMP < TR50%.

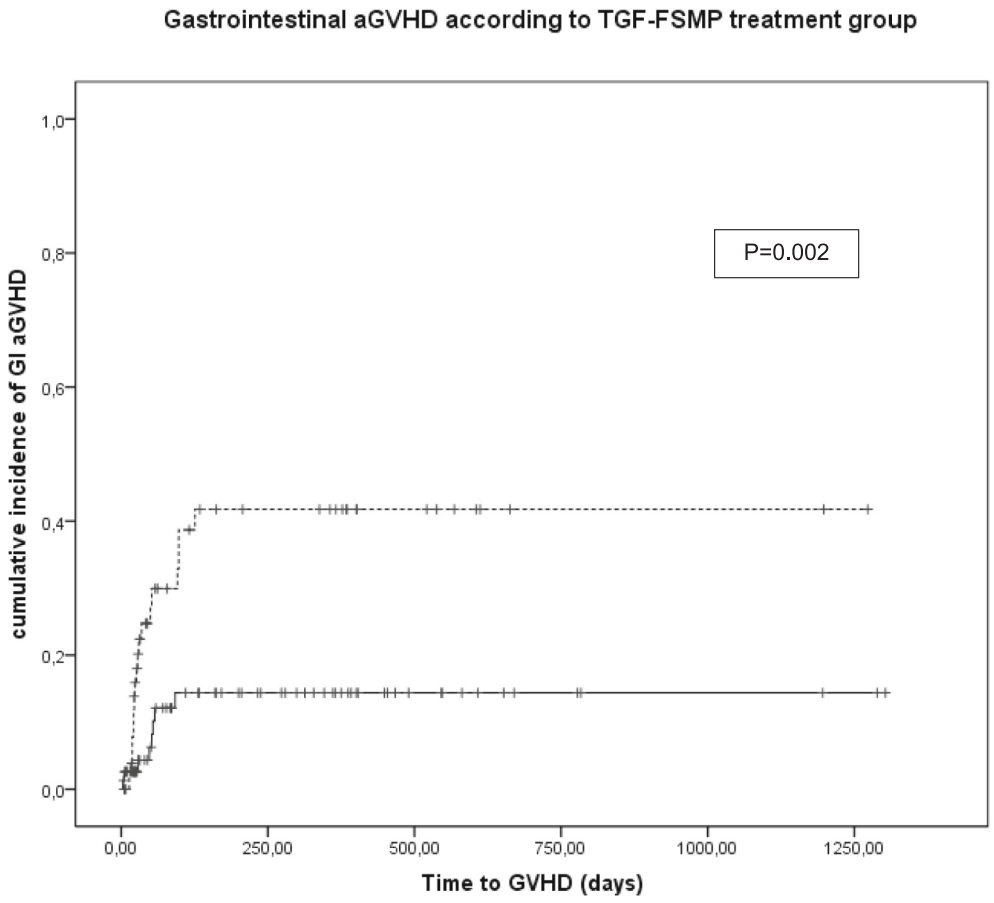

Fig. 3. Cumulative incidence of gastrointestinal aGVHD (any grade) according to treatment Group:
Group A - continuous line –assumption of TGF-FSMP ≥ TR50%
Group B – dotted line - assumption of TGF-FSMP < TR50%.

multivariable analysis (Cox regression for time dependent variables excluding patients transplanted twice), the increased risk of acute gastrointestinal GVHD was associated to disease status (advanced disease) $p = 0.003$, non-MUD donor ($p = 0.037$), and TGF-FSMP TR < 50% TGF-FSMP assumption ($p = 0.002$), while OS was significantly reduced by advanced disease status ($p = 0.014$), non-MUD donor ($p = 0.042$), < TR 50% of TFG-FSMP assumption (=0.044) and relapse (p = 0.000). According to Caocci et al. 12 ANN was performed to define the relative power of each variables on the selected clinical outcomes analyzed: malnutrition, acute and GI GVHD, pneumonia. TGF FSMP TR < 50% assumption was the most important one (100%) for all outcomes, with a higher AUC for malnutrition of 0.859.

4. Discussion

The study evaluated the impact of TGF-FSMP supplementation on nutritional status and other clinical outcomes, such as the incidence of severe and GI aGVHD, infections (pneumonia) and overall survival in a cohort of 133 consecutive patients submitted to allo-SCT between 2018 and 2023. The principal limitation of this study is that the cohort is selected according to patients' compliance on Modulen-IBD assumption and not from a controlled study, but the first study was designed to respect several principles that were reproduced in the extended cohort: firstly, the sufficient dose of TGF-FSMP was defined per protocol as at least the 50% of the prescribed dose and this principle was maintained in the whole cohort. Moreover, nutritional assessment was the primary outcome as defined per protocol and clinical characteristics were similar in the two groups (A and B) in the original study and in the extended cohort: most patients had AML and MDS, currently diseases with main indications for allo-SCT and were equally distributed in the pivotal study cohort of 51 patients as well as in the extended cohort of 82 patients. The two cohorts were comparable for demographic, clinical, hematological and transplant characteristics, even, in the extended cohort most patients had a matched-unrelated or haploidentical donor ($p = 0.015$) and for these reasons at higher transplant risk. All the patients were assessed for their nutritional status with PG-SGA [13]. No significant differences were observed in the PG-SGA A, B, and C distribution between the study and the extended cohorts and all of them received the same schedule of TGF-FSMP supplementation from admission until at least 28 days after transplant [8].

Based on the study plan, patients were evaluated by PG-SGA weekly and assessed for their nutritional status until day +28, according to the primary objective of the study.

As showed in the Fig. 1, the benefit of TGF-FSMP assumption appears to be dose-dependent, and an inverse correlation between the cumulative dose of TGF-FSMP and numeric PG-SGA score (representative of subjective malnutrition) after 28 days was found and confirmed in this larger cohort of patients.

Therefore, as previously reported in the pivotal study, the patients, according to TGF-FSMP treatment ratio (TR) were divided in two groups: Group A including the patients who had received TR ≥ 50% and Group B including those who assumed less than <50%.

Firstly, the comprehensive analysis on these 133 consecutives patients clearly confirms that the proportion of the malnourished patients (PG-SGA C) after 28 days from transplant is significantly higher ($p <$ 0.000) in Group B patients assuming less than <50% of TGF-FSMP, confirming the primary outcome of the pilot study.

The compliance in Modulen-IBD assumption was determined

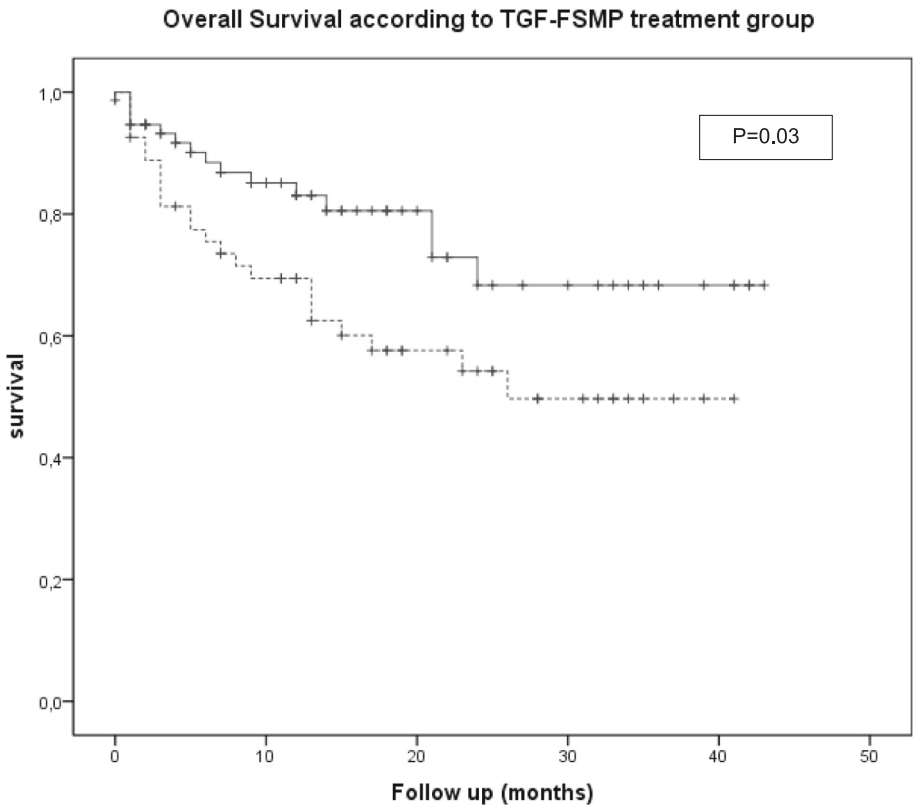

Fig. 4. OS according to treatment Group:
Group A - continuous line –assumption of TGF-FSMP ≥ TR50%
Group B dotted line - assumption of TGF-FSMP < TR50%)

principally by dysgeusia, diarrhea, nausea and vomiting that were correlated principally with clinical conditions and not with adverse events attributable to TGF-FSMP, as previously reported [8]. In the extended cohort compliance was slightly better than in the study cohort (mean TR 67.9% vs 62.5% respectively, $p = 0.031$).

Interestingly, ≥TR 50% of TGF-FSMP assumption was associated with a reduced risk of severe acute GVHD (grade II-IV MAGIC) and any grade gastrointestinal (GI) acute GVHD. These data confirmed on a larger cohort are firstly reported in literature.

This positive effect on GI GVHD could be due to the fact that TGF-beta contained in Modulen-IBD is able to sustain the trophism of intestinal epithelial cells and promote the Treg driven tolerance to self-antigens exposed due to the intestinal injury [14,15]. This possible explanation appears to be supported by a recent publication by Kaur et al. [16] reporting that a nutrient rich environment could activate intestinal epithelial cells to reprogram expression of TGF-beta that could expand regulatory T cells (Treg) in the lamina propria.

The systemic positive effect of Modulen-IBD on acute GVHD can be partially due to the reduction of GI GVHD but other factors could play a role, such as the modulation of microbiota and/or the significant reduction of pneumonia, but it should be further investigated in a larger prospective randomized trial.

Nevertheless, the reduction of malnutrition due to an "adequate" (≥TR 50%) assumption of TGF-FSMP appears to be strictly related to a reduction of the risk and incidence of GI GVHD and this effect could positively influence not only the GI microbiota "per se" but also the spread of dangerous bacteria from gastrointestinal tract [13,17]. This could explain why we observed a reduction of enteritis and sepsis (not significant) and pneumonia (significant).

This study confirms, in the multivariable analysis, the association between adequate assumption of Modulen-IBD and the main outcomes of alloSCT: malnutrition, severe acute GVHD, acute gastrointestinal GVHD and infections (pneumonia). Moreover, by using the artificial neural network (ANN) analysis performed to define the relative power of each variable on the selected clinical outcomes analyzed (malnutrition, acute GVHD, pneumonia) we found that the ≥TR 50% assumption of TGF-FSMP was was the most important one (100%) for all outcomes, with a higher AUC for malnutrition of 0.859.

Reducing the risk of such complications, a positive effect on survival can be expected and it is really observed. This is not surprising if we consider the observed positive effects all together. By multivariable analysis, OS was negatively affected by <TR 50% TGF-FSMP assumption, GI GVHD and advanced disease status on transplant and obviously by relapse.

However, the relapse incidence, appeared to be not affected by the assumption of TGF-FSMP: while the relapse incidence was not different in the Group A (21.1%) and in Group B (24.1%) ($p = 0.683$), the estimated median overall survival (OS) was significantly better in Group A (33 months) than in Group B (25.1 month) $p = 0.03$, as shown in Fig. 4.

Finally, two potential positive effects that could be discussed in terms of nutritional therapy appropriateness are the reduction in the use of parenteral nutrition, and the reduced hospital stay with consequent costs reduction.

In conclusion, nutritional supplementation with TGF-FSMP (Modulen-IBD) at ≥TR 50% of the prescribed dose is significantly associated with a reduced patients' malnutrition 28 days after transplant, a reduced incidence of severe acute GVHD, GI aGVHD and pneumonia, hospitalizations costs, and seems to significantly improve overall survival of the transplanted patients. Further prospective randomized studies are warranted to confirm these data, firstly reported here.

Declaration of Competing Interest

The authors declare that there are not conflicting interests.

Data availability

Data will be made available on request.

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