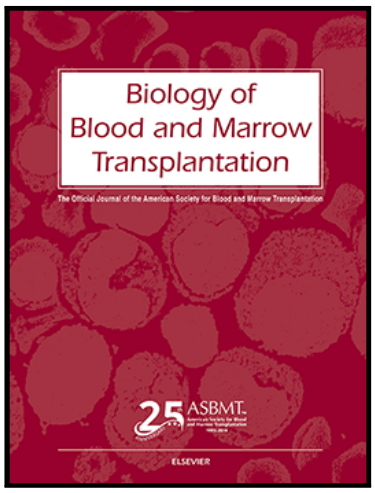


HAPLOIENTICAL TRANSPLANTS WITH POST-TRANSPLANT CYCLOPHOSPHAMIDE FOR RELAPSED/REFRACTORY HODGKIN LYMPHOMA: THE ROLE OF COMORBIDITY INDEX AND PRE-TRANSPLANT POSITRON EMISSION TOMOGRAPHY

C. Marani , A.M. Raiola , S. Morbelli , A. Dominietto , G. Ferrarazzo , D. Avenoso , L. Giannoni , R. Varaldo , F. Gualandi , C. Di Grazia , T. Lamparelli , S. Bregante , M.T. Van Lint , A. Ibatici , F. Bovis , R.M. Lemoli , M. Gobbi , A. Bacigalupo , E. Angelucci

PII: S1083-8791(18)30414-2
DOI: 10.1016/j.bbmt.2018.07.025
Reference: YBBMT 55207

To appear in: *Biology of Blood and Marrow Transplantation*

Received date: 19 March 2018
Accepted date: 15 July 2018

Please cite this article as: C. Marani , A.M. Raiola , S. Morbelli , A. Dominietto , G. Ferrarazzo , D. Avenoso , L. Giannoni , R. Varaldo , F. Gualandi , C. Di Grazia , T. Lamparelli , S. Bregante , M.T. Van Lint , A. Ibatici , F. Bovis , R.M. Lemoli , M. Gobbi , A. Bacigalupo , E. Angelucci , HAPLOIENTICAL TRANSPLANTS WITH POST-TRANSPLANT CYCLOPHOSPHAMIDE FOR RELAPSED/REFRACTORY HODGKIN LYMPHOMA: THE ROLE OF COMORBIDITY INDEX AND PRE-TRANSPLANT POSITRON EMISSION TOMOGRAPHY, *Biology of Blood and Marrow Transplantation* (2018), doi: 10.1016/j.bbmt.2018.07.025

Highlights

- Allogeneic transplantation is a valid approach for advanced Hodgkin Lymphoma
- Pre-transplant comorbidity have a great impact on transplant outcomes
- Pre-transplant functional imaging analysis predicts post-transplant relapse-rate
- Long lasting Hodgkin remissions have been observed in post-transplant relapses

HAPLOIENTICAL TRANSPLANTS WITH POST-TRANSPLANT CYCLOPHOSPHAMIDE FOR RELAPSED/REFRACTORY HODGKIN LYMPHOMA: THE ROLE OF COMORBIDITY INDEX AND PRE-TRANSPLANT POSITRON EMISSION TOMOGRAPHY

Marani C.[1,3], Raiola A.M.[1], Morbelli S.[2] Dominietto A.[1], Ferrarazzo G.[2], Avenoso D.[1,3], Giannoni L.[1], Varaldo R.[1], Gualandi F.[1], Di Grazia C.[1], Lamparelli T.[1], Bregante S.[1], Van Lint M.T.[1], Ibatici A.[1], , Bovis F.[4], Lemoli R.M.[3], Gobbi M.[3] Bacigalupo A. [5] and Angelucci E. [1]

1 Division of Haematology and Bone Marrow Transplantation, Policlinico San Martino, IRCCS per l'Oncologia, Genoa, Italy
2 Nuclear Medicine Unit, Department of Health Sciences, Policlinico San Martino, IRCCS per l'Oncologia, Genoa, Italy
3 Haematology Clinic, Department of Internal Medicine (DiMI), University of Genoa, Policlinico San Martino, IRCCS per l'Oncologia, Genoa, Italy
4 Biostatistics Unit, Department of Health Sciences (DISSAL), University of Genoa, Italy
5 Istituto di Ematologia, Policlinico Universitario A Gemelli, Università Cattolica, Roma, Italy

Keywords: Hodgkin lymphoma (HL); allogeneic transplant (HCT); post-transplant cyclophosphamide (PT-Cy); positron-emission tomography (PET)

SUMMARY

Background. Disease relapse remains an unmet medical need for patients with Hodgkin lymphoma (HL) receiving an allogeneic hematopoietic cell transplantation (HCT). **Methods.** With the aim of identifying patients at high risk for post-transplant relapse, we retrospectively reviewed 41 HL patients who had received haploidentical (haplo) non myeloablative (NMA) HCT with high dose post-transplant cyclophosphamide (PT-CY) for graft-versus-host (GvHD) prophylaxis. Primary

refractory disease, relapse within 6 months from autologous stem cell transplantation (ASCT), age, pre-transplant chemotherapy, hematopoietic cell transplantation comorbidity index (HCT-CI), sex mismatch, tumor burden and pre-transplant positron-emission tomography (FDG-PET) status, assessed by Deauville score, were analyzed as variables influencing outcomes.

Results. All but one patient engrafted: median time to neutrophil and platelet recovery were15 (range 13–23) and 19 (12–28) days, respectively. Cumulative incidence of severe (grade III-IV) acute GvHD and 3-year moderate-severe chronic GvHD was 2.4% and 11.8%, respectively. The 3-year overall (OS), progression free (PFS) and graft relapse free survival (GRFS) were 75.6%, 43.9%, and 39%, respectively. On multivariate analysis, 3-year OS was significantly worse in patients with HCT-CI ≥ 3 (HR 5.0 95% CI 1.1-21.8 p =0.03). Three-year relapse rate , 3-year PFS and 3-year GRFS were significantly worse in patients with HCT-CI ≥ 3 (HR=3.5 95% CI 1.3-9.3 p=0.01, HR=3.3 95% CI 1.2-9.0 p=0.02 and HR=4.2 95% CI 1.7-9.9 p=0.001, respectively) and in patients with a Deauville score ≥ 4 on pre-transplant FDG-PET (HR=4.4 95% CI 1.6-12.4 p=0.005, HR=3.8 95% CI 1.5-9.7 p=0.005 and 3.2 95% CI 1.3-7.9 p=0.01, respectively). On univariate analysis, 3-year NRM was significantly worse only in patients with a HCT-CI ≥ 3 (HR=17.6 95% CI 1.4-221.0). **Conclusions.** Among relapsed/refractory HL patients undergoing haplo NMA HCT with PT-Cy, pre-transplant FDG-PET with a Deauville score ≥ 4 and HCT-CI ≥ 3 identified patients at high risk of relapse. Moreover, a HCT-CI ≥ 3 was associated with higher NRM and lower OS.

BACKGROUND

Althought the majority of patients with Hodgkin lymphoma (HL) are cured by frontline combination chemotherapy, around 10-20% will require further therapy for relapse or refractory disease [1]. Salvage chemotherapy followed by high-dose chemotherapy with autologous stem cells transplantation (ASCT) is the gold standard treatment producing long-term remissions in approximately 40–50% of relapsed patients [2]. However, relapse after ASCT is challenging, with a reported median survival after ASCT failure ranging between 7.3 and 25 months [3].

Both American and European Society for Blood and Marrow Transplantation currently recommend allogeneic hematopoieic transplantation (HCT) as the prefered strategy in eligible HL patients with chemosensitive relapse after ASCT and an available compatible donor [4, 5], whereas, for patients without either HLA identical donors or matched unrelated donor (MUD), growing evidence indicates the efficacy and feasibility of HLA haploidentical transplantation with post-transplant cyclophosphamide (PT-CY) [6 - 8].

However, relapse remains a significant cause of HCT failure [1, 6 – 8]. In this setting, the early identification of patients at high risk of relapse, it is the first step to conceive risk-adapted strategies aiming to reduce disease recurrence and increase survival. Here, we report the clinical outcome and predictive factors for relapse of 41 consecutive relapsed/refractory HL patients submitted to NMA haploidentical HCT with PT-CY at our Center.

METHODS

Forty-four consecutive patients with HL received a NMA allograft from HLA-haploidentical related donors between September 2009 and June 2015 at our institution. Three patients with no positron-emission tomography (FDG-PET) status at time of haplo HCT were excluded from data analysis. Overall, outcomes of 41 HL patients receiving a haplo HCT were analyzed. All patients were treated on institutional protocol that was approved by the institutional review board of the study site. No exclusion criteria were used for disease status or chemosensivity. Primary refractory disease, relapse within 6 months from ASCT [1], age, number of pre-transplant chemotherapy lines, HCT-CI [38], sex mismatch, tumor burden (defined as tumor stage at diagnosis; I-IIA vs IIB-IV) and pre-transplant positron-emission tomography (FDG-PET) status, assessed by Deauville score [9 - 12], were analyzed as variables influencing outcomes. In surviving patients follow-up data were censored at time of follow-up analysis, that is on October 4th 2016 and at the diagnosis of engraft failure in patients who failed the HCT. All patients signed consent forms approved by the institutional review board.

<u>Conditioning regimen GVHD prophylaxis</u>

All patients received a non-myeloablative regimen consisting of cyclophosphamide (Cy) 14.5 mg/kg on days - 6 and - 5, fludarabine 30 mg/sqm/day from day - 6 to day -2 and low dose TBI (2 Gy) on day – 1 [7]. GVHD prophylaxis consisted of post- transplant high-dose of Cy (50 mg/kg) on days +3 and +4 ; cyclosporine 1.5mg/kg/day (and then adjusted, accordingly to a blood level target between 200 and 400 microg/L) started at day + 5 as continuous infusion, switched as twice /day oral administration at patient discharge and then tapered from day + 100 or on opinion of treating physician in case of GVHD, disease progression and mixed-chimera; mycophenolate mofetil 15 mg/kg bid from day +5 until day + 30. Peg-filgrastim 6 mg (Neulasta, Amgen, Thousand Oaks, CA) single dose was administered by subcutaneous injection on day +6.

Stem cell source

Unmanipulated bone marrow was the stem cell source in all the patients on day 0. Donors underwent BM harvest under general anesthesia, and the ideal target of mononuclear cells was 4 x 10^8/kg. [7]

Donor

Family donors, 24 males and 20 females, were all genotypically HLA haploidentical, typed on A, B, C and DRB1. Donor/recipient sex was matched in the 50% of cases [37].

Supportive care

Antimicrobial/fungal prophylaxis and treatment were administered as previously described [7] as well as CMV, EBV, HHV-6 and frequent viral infection (e.g. influential, respiratory syncytial virus) monitoring and treatment. [7]

18F-FDG PET/CT acquisition

All the patients underwent preparation and fluorodeoxyglucose-positron emission tomography (FDG PET/CT) according to European guidelines [12] and data were acquired using a 16-slices PET/CT hybrid system (Biograph 16, Siemens Medical Solutions, Knoxville TN, USA).

Images Analysis

Residual metabolic activity before HCT was assessed by FDG-PET. When available for central reviewing, pre-transplant FDG-PET scans were evaluated at Nuclear Medicine Unit of our institution, in keeping with the consensus recommendations, by means of the Deauville 5-point score [13 - 16]; thus sites of residual uptake before allograft were compared to the uptake in the normal mediastinal blood pool and the liver as follows: Score 1, no uptake; Score 2, uptake ≤ mediastinum; Score 3, uptake > mediastinum and ≤ liver; Score 4, uptake moderately increased above liver at any site; Score 5, markedly increased uptake above liver and/or new sites of disease. A Deauville score 4 or greater was considered as FDG-PET positive. When FDG-PET images were not available for central reviewing, pre-transplant FDG-PET status was established on the bases of original local report (see results section for further details)

FDG-PET status before NMA allograft

All 41 patients were stratified accordingly to pre-transplant FDG-PET results. In 32 (78%) out of 41 patients, pre-transplant FDG-PET scans were centrally reviewed; whereas in the remaining 9 patients, clinical charts were reviewed to assess pre-transplant status: patients with residual metabolic activity and clearly clinical progressive (5/9 patients) disease were accounted FDG-PET positive; asymptomatic patients with complete negative FDG-PET (4/9 patients) report were considered FDG-PET negative. Nineteen (46%) out of 41 patients underwent HCT with a

FDG-PET negative scan (Deauville < 4); 22 of 41 (54%) with FDG-PET positive scan (Deauville ≥ 4).

Follow-up and post NMA allograft therapy for relapsed/progressive disease

After 2 months from transplantation, FDG-PET evaluation was performed; subsequent scans were decided on physician discretion. The development of new FDG-avid lesions in the absence of other potential causative pathologies, or 'significant' increase in Standardized Uptake Value (SUV) of over 25% in previously positive lesions was considered compatible with relapse/progression. Relapse was confirmed by histological study if biopsy was feasible; otherwise a FDG-PET/CT studies were repeated at 6–8 weeks to confirm progression.

Patients experiencing relapse were eligible for chemotherapy by treating physician (mainly rituximab 375 mg/mq day 1 and bendamustine 90 mg/mq days 1 -2; in selected cases, gemcitabine, brentuximab vedotin, nivolumab, involved-field radiotherapy (RT) and donor lymphocyte infusion (DLI) were used. Dose of DLI started at 1 x10^3/kg CD3+ cells and was increased every 1–2 months by half log, up to 1 x10^7/kg. Patients with mixed-chimeras, as assessed by PCR analysis of short tandem-repeat loci, were treated with cyclosporine withdrawal or DLI.

Statistical Analysis

Primary refractory HL was defined as progression or no complete remission after front-line treatment. Salvage chemotherapy with subsequent ASCT was, overall, considered one line of therapy. Radiotherapy was considered as line of therapy if used for localized relapsed disease; it was considered as part of the chemotherapy if used as consolidation for bulky mass. Neutrophil recovery was considered a neutrophil count ≥ 0.5 x 109/L for more than 2 consecutive days without G-CSF support); platelet recovery was considered a platelet count ≥ 20 x 109/L for more than 2 consecutive days without transfusions. GvHD diagnosis and clinical grading were performed as described literature [17; 18]. Non-relapse mortality (NRM) was defined as death without disease

recurrence or persistence. When estimating cumulative incidence, relapse was a competing risk for non-relapse mortality (and vice versa). GRFS is a novel composite end point recently proposed [33; 34] in the evaluation of both standard and novel transplant platform. GRFS events were defined as grade 3-4 acute GVHD, chronic GVHD requiring systemic immunosuppressive treatment, disease relapse, or death from any cause. Kaplan-Meier estimates were used to determine the unadjusted probability of overall survival (OS), progression free survival (PFS) and GRFS among patients who underwent FDG-PET with differences between the curves determined using log-rank tests.

Continuous variables are presented as median (1st-3rd quartiles), whereas categorical variables are presented as frequencies. Statistical comparisons across categorical factors, not including time-to-event data, were completed with the χ-square test. Continuous factors were compared by the U-Mann-Whitney test for nonparametric data. Cox univariate and multivariate regression model was performed to identify pre-transplant factors influencing outcomes. Only factors significantly associated with outcome in univariate analysis were included in a multivariate model following a stepwise procedure.

Fine and Gray model for competing risks [19; 20] was used to assess the impact of FDG-PET on the study outcomes. Sub-distribution hazard ratio (SHR) and relative 95% confidence intervals (CI) were shown for Fine and Gray model. Cumulative incidences with competing risk analysis [21] were calculated for relapse, non-relapse mortality, acute and chronic GVHD. Graft failure, relapse, and death were considered competing events when estimating the cumulative incidence of GVHD. Values of $P < 0.05$ were considered statistically significant. All analyses were performed using SAS version 9.3 (SAS Institute, Cary, NC) and R.

RESULTS

Patient characteristics are reported in Table 1. This study enrolled heavily pre-treated HL patients with at least 3 conventional chemotherapy lines before HCT. Most of them (30 out of 41; 73%) were refractory to front-line chemotherapy. Front-line therapy were ABVD (adriamycin,

bleomycin, vinblastine, dacarbazine) regimens in almost all case. Salvage chemotherapy for relapsed/refractory disease were IGEV (ifosfamide, gemcitabine, vinorelbine, and prednisolone) DHAP/DHAOX (dexamethasone, cisplatin/oxaliplatin, and cytarabine) or BEACOPP/BEACOPPescaleted (bleomycin, etoposide, adriamycin, cyclophosphamide, vincristine, prednisone) regimens in most of case. Twenty-six of 41 (63%) patients were exposed to radiotherapy, either as consolidation on bulky disease or as regional treatment of relapse. Twenty-two of 41 (54%) had received brentuximab vedotin and 40 of 41 (97%) had been submitted to ASCT. Five patients underwent to tandem transplantation with haplo transplantation performed after a median time of 96 days (range 78-166) from ASCT. No patient was exposed to checkpoint inhibitor therapy prior of haplo transplant.

Engraftment

All but 1 patient engrafted; the patients who failed allogeneic transplant showed autologous neutrophil and platelet recovery after re-infusion of cryopreserved autologous stem cells. Median times to neutrophil and platelet recovery were respectively 15 days (range 13–23) and 19 (12–28). All patients were evaluable for chimerism from day +30 post-transplant on unfractionated marrow cells, as well as on peripheral blood CD3+ selected cells. Four (10%) out of 41 patients were mixed chimeras (7–21% recipient). All converted to full donor status (0% recipient) in subsequent chimerism follow-up assessment. In 1 out of 4 patients with a mixed chimeras (21% recipient) cyclosporine was halved on day 53 from transplant. In the other 3 patients with mixed-chimeras (7-10% recipient) no interventions were adopted.

GVHD

The 100-day cumulative incidences of acute GVHD of grade II–IV was 20.7% (95%CI: 19.9%-21.6%). Severe acute GVHD of grade III-IV was diagnosed in only one patient (the event

occurred after 27 days). The 100-day cumulative incidences of acute GVHD of grade III–IV was 2.4% (95%CI: 2.3%-2.6%).

Overall, 5 patients developed chronic GVHD of grade moderate-severe, with a 3-year cumulative incidence of 11.8% (95%CI: 11.1%-12.5%). Sites of cGVHD were skin (2 patients), lung (2 patients) and both skin and lung in the other patient. All five patients were treated with steroids 1 mg/kg; two patients received also mycophenolate mofetil; one cyclosporine; and one extracorporeal photopheresis. None of the five patients were exposed to checkpoint inhibitor prior of GVHD

NRM, PFS, GRFS and OS

Median follow-up for surviving patients was 3.25 years (range 1.29 – 7.06); 3-year cumulative incidence of NRM was 7.5% (95%CI: 7.0%-8.1%) (Figure 1c). Causes of NRM were cGVHD, myocarditis and pneumonia and occurred respectively at 8, 16 and 51 months from HCT. Overall, relapse/progression was diagnosed in 20 patients, resulting in a 3-year cumulative incidence of relapse of 55.4% (95%CI: 53.8%-57.0%) (Figure 1d). Median time to relapse was 9 months (5 - 14). Seven relapses were histologically documented whereas in 13 patients, relapses were diagnosed with imaging analysis as described in M and M. Seven patients (35%) died of progressive disease; 7 (35%) are currently off-therapy in clinical and radiological remission and 6 (30%) with ongoing therapy. The most commonly used therapy for post HCT relapse was a combination of immune-chemotherapy and DLI. Thirteen patients received R-Bendamustine and DLI; among them 5 patients received also brentuximab vedotin, 2 patients radiotherapy, and 1 patient nivolumab. The remaining 6 patients were treated with chemotherapy and/or radiotherapy without the use of DLI.

Eighteen out of 41 patients (43%) are in continuous complete remission after HCT.

Overall, Kaplan-Meier estimates for 3-year OS, PFS and GRFS were 75.6%, 43.9% and 39%, respectively (Figure 2). Outcomes analysis accordingly to pre-transplant variables is shown on table n. 3 and 4; and on figure 3 and 4.

Univariate analysis

On univariate analysis, 3-year NRM was significantly worse only in patients with a HCT-CI of 3 or greater (HR=17.6 95% CI 1.4-221.0). Pre-transplant FDG-PET did not impact on acute GVHD (HR=0.9; 95%CI: 0.5-1.8; p=0.86), chronic GVHD (HR=1.3; 95%CI: 0.2-7.0; p=0.79) and on 3-year overall survival (HR=2.0; 95%CI: 0.5-7.8; p=0.31).

Multivariate Cox analysis

In a multivariate Cox analysis, the 3-year OS was significantly worse in patients with HCT-CI of 3 or greater (HR 5.0 95% CI 1.1-21.8 p =0.03). Three-year relapse rate , 3-year PFS and 3-year GRFS were significantly worse in patients with HCT-CI of 3 or greater (HR=3.5 95% CI 1.3-9.3 p=0.01, HR=3.3 95% CI 1.2-9.0 p=0.02 and HR=4.2 95% CI 1.7-9.9 p=0.001, respectively) and in patients with a Deauville score of 4 or greater on pre-transplant FDG-PET (HR=4.4 95% CI 1.6-12.4 p=0.005, HR=3.8 95% CI 1.5-9.7 p=0.005 and 3.2 95% CI 1.3-7.9 p=0.01, respectively). Of note, all 5 patients treated according to tandem strategy achieved CR after ASCT and underwent to HCT with a negative FDG-PET scan (Deaville score ≤ 3). However, 2/5 patients relapsed at 5 and 12 months after transplant.

Value of the first post HCT FDG-PET scan

Thirty-eight post-transplant FDG-PET scans were available for central reviewing. The median time of the first post-transplant FDG-PET assessment was 66 days (51-76). The FDG-PET scan was negative in 35 out of 38 (92%) and positive in 3 out 38 (8%) patients. In these patients, pre-transplant FDG-PET was positive in two subjects who subsequently died for progressive disease. The third patient, who had a negative pre-transplant FDG-PET, was treated for disease relapse, and is still alive after 364 days after transplant.

Among 35 patients with a negative post-transplant FDG-PET, 14 (40%) relapsed. Regarding the predictive value of post-transplant imaging, the calculated negative predictive value of a negative FDG-PET scan was just 60% (95% CI 54.6% - 65.1%).

DISCUSSION

We confirm, here, the feasibility and the efficacy of NMA haplo transplant in heavily pre-treated HL patients. The transplant procedure was well tolerated with high rate of engraftment, low incidence of GVHD and NRM as shown in with previous papers [6 – 8]. Indeed, the graft-versus-lymphoma effect may overcome the chemo-refractoriness of the disease allowing to reach a 3 years OS and PFS of 75.6% and 43.9%, respectively, supporting the role of allogeneic transplantation in advanced disease [6 - 8; 22]. In our single center analysis, having a HCT-CI of 3 or greater was the only factor influencing OS. In our study, most of the comorbidity influencing the HCT-CI value were results of toxicity of previous treatment, as showed on univariate analysis where pre-transplant chemotherapy burden was the only other significant factor associated with a worse OS. This result, although to be confirmed in other studies, should raise question on the timing of HCT procedure and advocate a more comprehensive and collegial approach between chemotherapy wards and transplant center. Moreover, having a HCT-CI ≥ 3 and a Deauville score ≥ 4 on pre-transplant FDG-PET were associated with higher relapse rate, lower PFS and GRFS. Whereas in the autograft setting the role of pre-transplant FDG-PET is well established [23 - 27], few and discordant papers have been published on FDG-PET assessment before allograft [9 – 12]. Moreover, previous studies have addressed this issue either on heterogeneous patient's population [9] or on hematological malignancies other than Hodgkin lymphoma [10 -12]. Recently, Reyal et al., published the results of a large multicenter and retrospective study on HL patients undergoing a myeloablative, T Cell-Depleted Allogeneic Transplantation [28]. In that paper, the role of pre-transplant FDG-PET was questioned. However, the platform used to perform HCT was significantly different (e.g. T-cell depletion, more intense conditioning regimen). On the other hand, if our results will be confirmed in other reports, FDG-PET status before an NMA allograft might be

one of criteria to consider tailoring post-transplant immunemodulation, such as early cyclosporine withdrawal or prophylactic post-transplant therapy with DLI and checkpoint inhibitors. Moreover, our study highlighted that patients relapsing after a NMA allograft, might still achieve long lasting remission with immune-chemotherapy, IF-RT, immune checkpoint inhibitor and DLI [35]. We also found that the first post-transplant FDG-PET had a low negative predictive value for disease relapse. The standard practice of performing post-transplant FDG-PET follow-up, especially for those patients in complete metabolic remission before transplantation, might be challenged.

The main limit of our study is the retrospective nature of the analysis and the various chemotherapy strategies used before transplantation. The great variability of salvage therapy used and the reference, on a national basis, of patients from other centers than our, not allowed us to properly assess the quality of response to salvage chemotherapy. Given the significant prognostic value of “chemosensitive” and “chemorefractory” cathegories [36] in HL population, we hope that future clinical trials will be able to correlate quality of response after salvage chemotherapy with pre-transplant FDG-PET Deauville score, to design early strategies of post-transplant immunomodulation.

In conclusion, we suggest the potential role of PET and HCT-CI before NMA haplo transplant to identify a patient population at high risk for early relapse and/or transplant failure . This hypothesis should be investigated in a prospective, multicenter study integrating novel strategies of relapse prevention.

Acknowledgment

Carlo Marani would like to acknowledge Barbara Bruno, Segreteria Nazionale GITMO, for her support on data collection and analysis

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

Carlo Marani received doctoral scholarship as part of his PhD program at the University of Genoa.

BIBLOGRAPHY

1. Reddy NM, Perales MA. Stem cell transplantation in Hodgkin lymphoma. Hematol Oncol Clin North Am. 2014 Dec;28(6):1097-112.

2. Rashidi A, Ebadi M, Cashen AF. Allogeneic hematopoietic stem cell transplantation in Hodgkin lymphoma: a systematic review and meta-analysis. Bone Marrow Transplant. 2016 Apr;51(4):521-8.

3. Moskowitz AJ, Perales MA, Kewalramani T, et al. Outcomes for patients who fail high dose chemoradiotherapy and autologous stem cell rescue for relapsed and primary refractory Hodgkin lymphoma. Br J Haematol. 2009 Jul;146(2):158-63.

4. Perales MA, Ceberio I, Armand P et al. Role of cytotoxic therapy with hematopoietic cell transplantation in the treatment of Hodgkin lymphoma: guidelines from the American Society for Blood and Marrow Transplantation. Biol Blood Marrow Transplant 2015; 21: 971–983.

5. Sureda A, Bader P, Cesaro S et al. Indications for allo- and auto-SCT for haematological diseases, solid tumours and immune disorders: current practice in Europe, 2015. Bone Marrow Transplant 2015; 50: 1037–1056.

6. Burroughs LM, O'Donnell PV, Sandmaier BM, et al. Comparison of outcomes of HLA-matched related, unrelated, or HLA-haploidentical related hematopoietic cell transplantation following nonmyeloablative conditioning for relapsed or refractory Hodgkin lymphoma. Biol Blood Marrow Transplant. 2008 Nov;14(11):1279-87.

7. Raiola A, Dominietto A, Varaldo R, et al. Unmanipulated haploidentical BMT following non-myeloablative conditioning and post-transplantation CY for advanced Hodgkin's lymphoma. Bone Marrow Transplant. 2014 Feb;49(2):190-4.

8. Castagna L, Bramanti S, Devillier R, et al. Haploidentical transplantation with post-infusion cyclophosphamide in advanced Hodgkin lymphoma. Bone Marrow Transplant. 2017 May;52(5):683-688.

9. Dodero A, Crocchiolo R, Patriarca F, et al. Pretransplantation [18-F]fluorodeoxyglucose positron emission tomography scan predicts outcome in patients with recurrent Hodgkin lymphoma or aggressive non-Hodgkin lymphoma undergoing reduced-intensity conditioning followed by allogeneic stem cell transplantation. Cancer. 2010 Nov 1;116(21):5001-11

10. Sauter CS, Lechner L, Scordo M, et al. Pretransplantation fluorine-18-deoxyglucose--positron emission tomography scan lacks prognostic value in chemosensitive B cell non-hodgkin lymphoma patients undergoing nonmyeloablative allogeneic stem cell transplantation. Biol Blood Marrow Transplant. 2014 Jun;20(6):881-4

11. Bachanova V, Cao Q, Ustun C et al. Pretransplantation fluorine-18-deoxyglucose-positron emission tomography scan has no influence on relapse and survival in non-Hodgkin lymphoma patients undergoing allo-SCT. Bone Marrow Transplant. 2015 Jan; 50(1):142-4.

12. Ulaner GA, Goldman DA, Sauter CS, et al. Prognostic Value of FDG PET/CT before Allogeneic and Autologous Stem Cell Transplantation for Aggressive Lymphoma. Radiology. 2015 Nov;277(2):518-26.

13. Boellaard R, Delgado-Bolton R, Oyen WJ, et al. European Association of Nuclear Medicine (EANM). FDG PET/CT: EANM procedure guidelines for tumor imaging: version 2.0. Eur J Nucl Med Mol Imaging. 2015 Feb;42(2):328-54

14. Barrington SF, Mikhaeel NG, Kostakoglu L et al. Role of imaging in the staging and response assessment of lymphoma: consensus of the International Conference on Malignant Lymphomas Imaging Working Group. J Clin Oncol. 2014 Sep 20;32(27):3048-58.

15. Cheson BD, Fisher RI, Barrington SF et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. J Clin Oncol. 2014 Sep 20;32(27):3059-68.

16. Johnson SA, Kumar A, Matasar MJ et al. Imaging for Staging and Response Assessment in Lymphoma. Radiology. 2015 Aug;276(2):323-38. doi: 10.1148/radiol.2015142088.

17. Jagasia MH, Greinix HT, Arora M, et al. National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease: I. The 2014 Diagnosis and Staging Working Group report. Biol Blood Marrow Transplant. 2015 Mar;21(3):389-401

18. Harris AC, Young R, Devine S, et al. International, Multicenter Standardization of Acute Graft-versus-Host Disease Clinical Data Collection: A Report from the Mount Sinai Acute GVHD International Consortium. Biol Blood Marrow Transplant. 2016 Jan;22(1):4-10.

19. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. J Am Stat Assoc 2011; 94: 496 – 509

20. Kalbfleisch JD, Prentice HM. The Statistical Analysis of Failure Time Data. New York: Wiley, 1980

21. Putter H, Fiocco M, Geskus RB. Tutorial in biostatistics: competing risks and multistate models. Stat Med 2007; 26: 2389 – 2430

22. Thomson KJ, Kayani I, Ardeshna K et al. A response-adjusted PET-based transplantation strategy in primary resistant and relapsed Hodgkin Lymphoma. Leukemia. 2013 Jun;27(6):1419-22

23. Jabbour E, Hosing C, Ayers G, et al. Pretransplant positive positron emission tomography/gallium scans predict poor outcome in patients with recurrent/refractory Hodgkin lymphoma. Cancer. 2007 Jun 15;109(12):2481-9

24. Moskowitz CH1, Matasar MJ, Zelenetz AD, et al. Normalization of pre-ASCT, FDG-PET imaging with second-line, non-cross-resistant, chemotherapy programs improves event-free survival in patients with Hodgkin lymphoma. Blood. 2012 Feb 16;119(7):1665-70.

25. Moskowitz AJ1, Yahalom J, Kewalramani T, et al. Pretransplantation functional imaging predicts outcome following autologous stem cell transplantation for relapsed and refractory Hodgkin lymphoma. Blood. 2010 Dec 2;116(23):4934-7.

26. Poulou LS1, Thanos L, Ziakas PD. Unifying the predictive value of pretransplant FDG PET in patients with lymphoma: a review and meta-analysis of published trials. Eur J Nucl Med Mol Imaging. 2010

27. Adams HJ, Kwee TC. Prognostic value of pretransplant FDG-PET in refractory/relapsed Hodgkin lymphoma treated with autologous stem cell transplantation: systematic review and meta-analysis. Ann Hematol. 2016 Apr;95(5):695-706

28. Reyal Y, Kayani I, Bloor AJ, et al. Impact of Pretransplantation (18)F-Fluorodeoxyglucose-Positron Emission Tomography on Survival Outcomes after T Cell-Depleted Allogeneic Transplantation for Hodgkin Lymphoma. Biol Blood Marrow Transplant. 2016 Jul;22(7):1234-41.

29. Genadieva-Stavrik S, Boumendil A, Dreger P, et al. Myeloablative versus reduced intensity allogeneic stem cell transplantation for relapsed/refractory Hodgkin's lymphoma in recent years: a retrospective analysis of the Lymphoma Working Party of the European Group for Blood and Marrow Transplantation. Ann Oncol. 2016 Dec;27(12):2251-2257.

30. Merryman RW, Kim HT, Zinzani PL, et al. Safety and efficacy of allogeneic hematopoietic stem cell transplant after PD-1 blockade in relapsed/ refractory lymphoma. Blood 2017;129:1380–1388

31. Herbaux C, Gauthier J, Brice P, et al. Nivolumab is effective and reasonably safe in relapsed or refractory Hodgkin's lymphoma after allogeneic hematopoietic cell transplantation: a study from the Lysa and SFGM-TC [abstract]. Blood 2015;126: Abstract 3979.

32. Gordon LI. Strategies for Management of Relapsed or Refractory Hodgkin Lymphoma. J Natl Compr Canc Netw. 2017 May;15(5S):716-718.

33. Holtan SG1, DeFor TE2, Lazaryan A1, et al. Composite end point of graft-versus-host disease-free, relapse-free survival after allogeneic hematopoietic cell transplantation. Blood. 2015 Feb 19;125(8):1333-8.

34. McCurdy SR1, Kasamon YL1, Kanakry CG1, et al. Comparable composite endpoints after HLA-matched and HLA-haploidentical transplantation with post-transplantation cyclophosphamide. Haematologica. 2017 Feb;102(2):391-400.

35. Ghiso A, Raiola AM, Gualandi F. DLI after haploidentical BMT with post-transplant CY. Bone Marrow Transplant. 2015 Jan;50(1):56-61

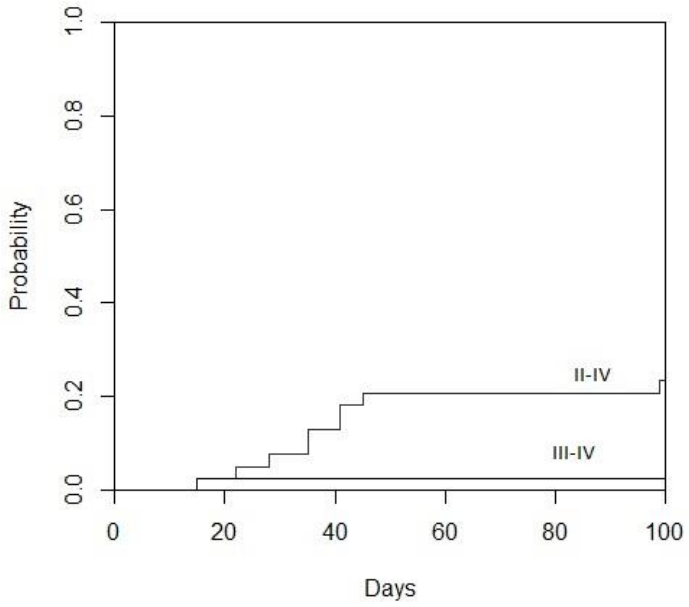
36. Sureda A, Canals C, Arranz R. 8. Allogeneic stem cell transplantation after reduced intensity conditioning in patients with relapsed or refractory Hodgkin's lymphoma. Results of the HDR-ALLO study - a prospective clinical trial by the Grupo Español de Linfomas/Trasplante de Médula Osea (GEL/TAMO) and the Lymphoma Working Party of the European Group for Blood and Marrow Transplantation. Haematologica. 2012 Feb;97(2):310-7.

37. Raiola AM, Risitano A, Sacchi N et al. Impact of HLA Disparity in Haploidentical Bone Marrow Transplantation Followed by High-Dose Cyclophosphamide. Biol Blood Marrow Transplant. 2018 Jan;24(1):119-126

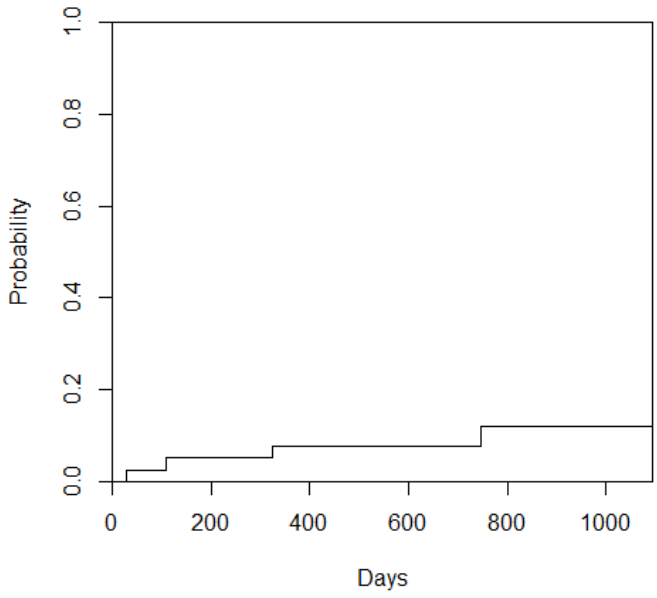
38. Sorror ML, Maris MB, Storb R et al. Hematopoietic cell transplantation (HCT)-specific comorbidity index: a new tool for risk assessment before allogeneic HCT. Blood 2015 Oct; 106 (8): 2912-2919

Figure 1: Cumulative incidence of outcomes in all 41 patients. A) acute GVHD. B) chronic GVHD. C) non-relapse mortality (NRM). D) relapse rate

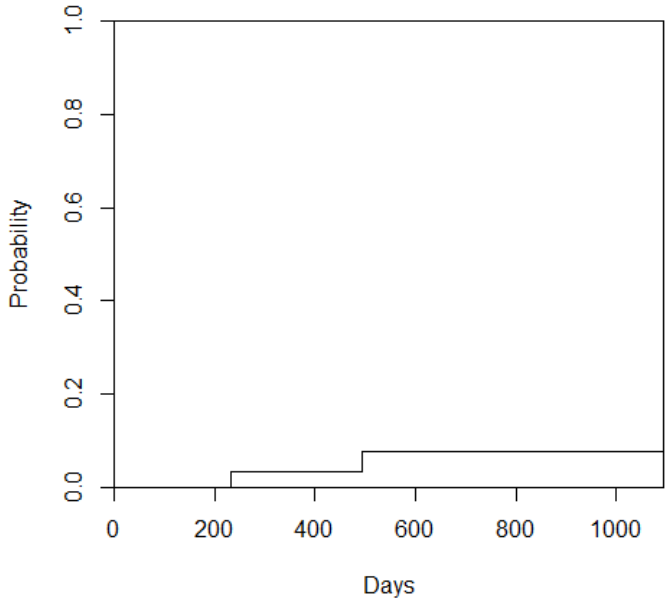
A) acute GVHD



B) chronic GVHD



C) NRM



D) relapse rate

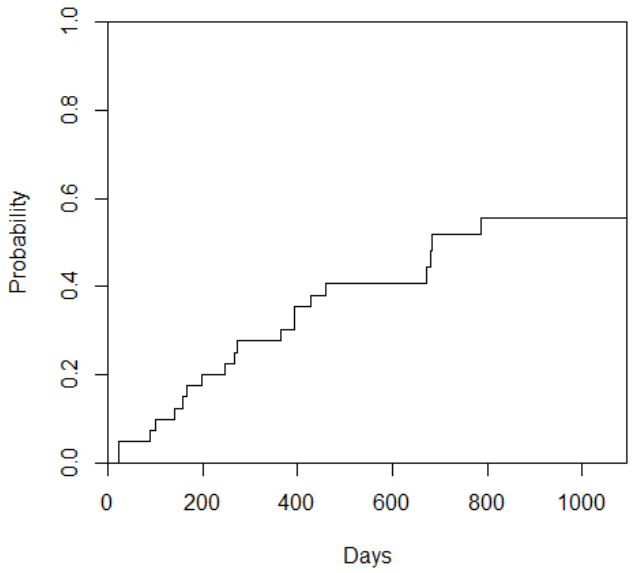


Figure 2: Kaplan-Meier estimates of overall survival (OS), progression free survival (PFS) and graft relapse free survival (GRFS)

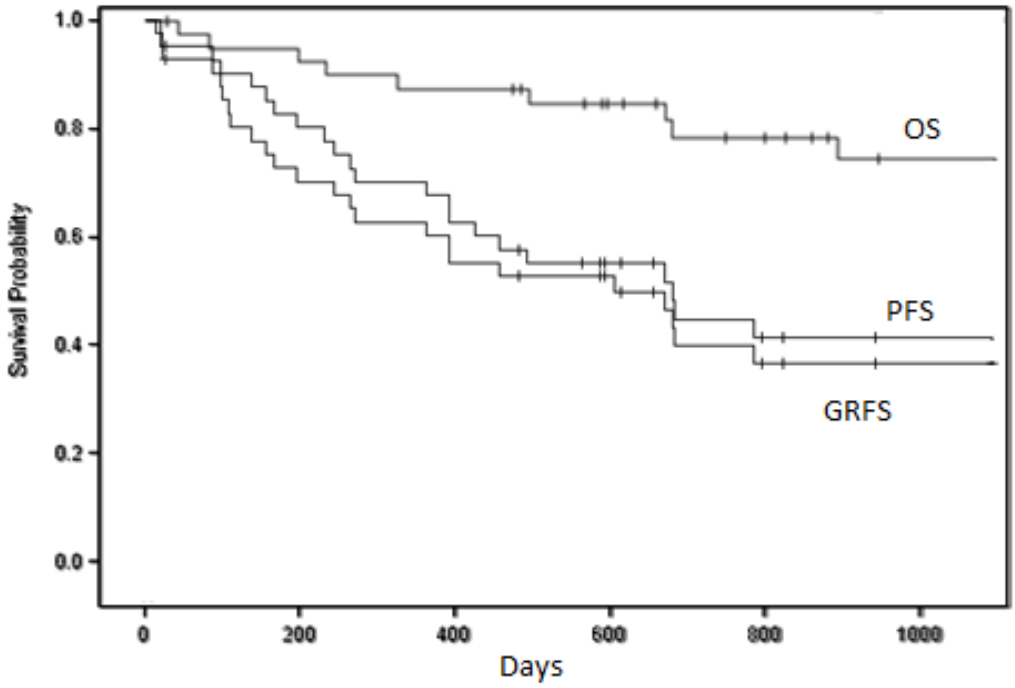


Figure 3: Cumulative incidence of disease relapse accordingly to pre-transplant FDG-PET status (positive if Deauville score ≥ 4)

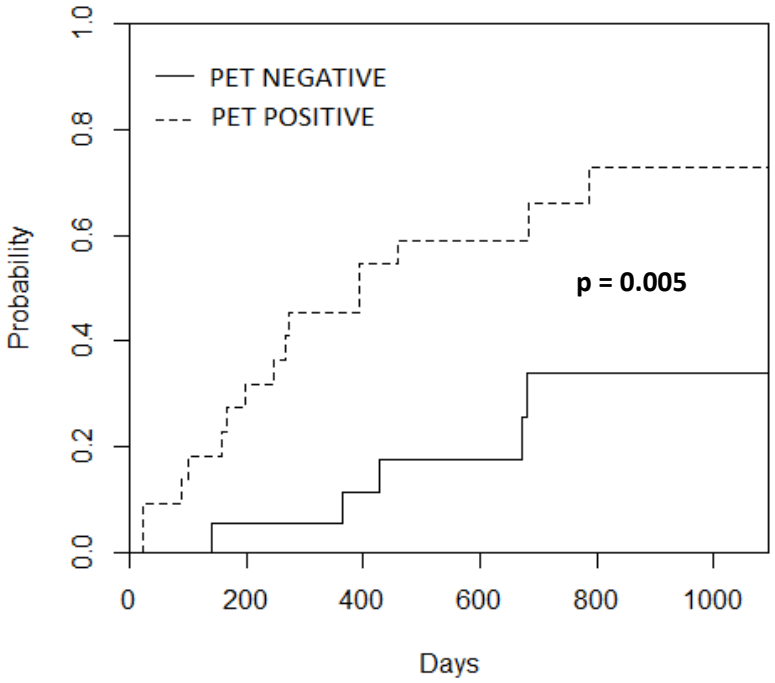
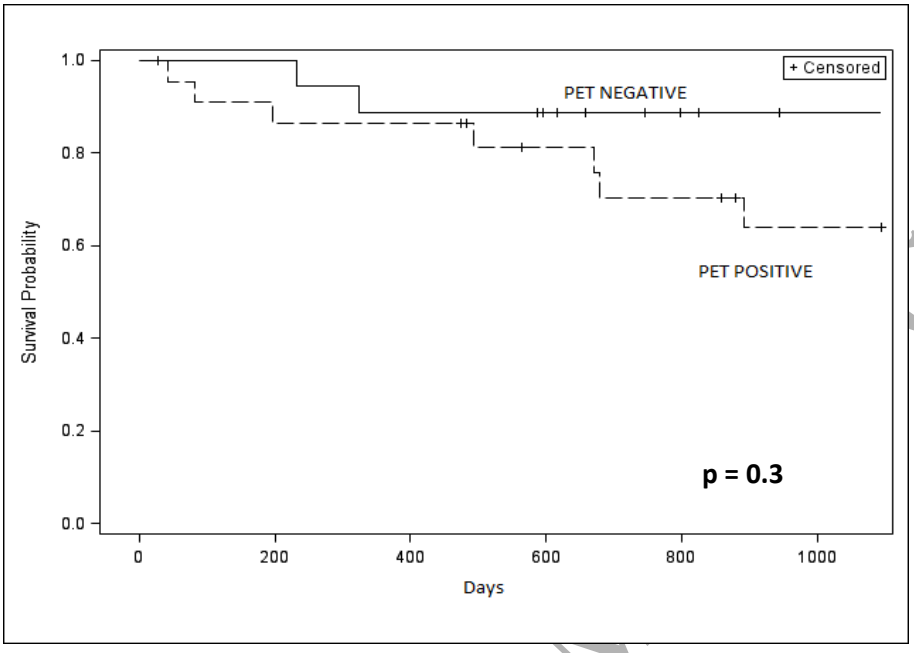
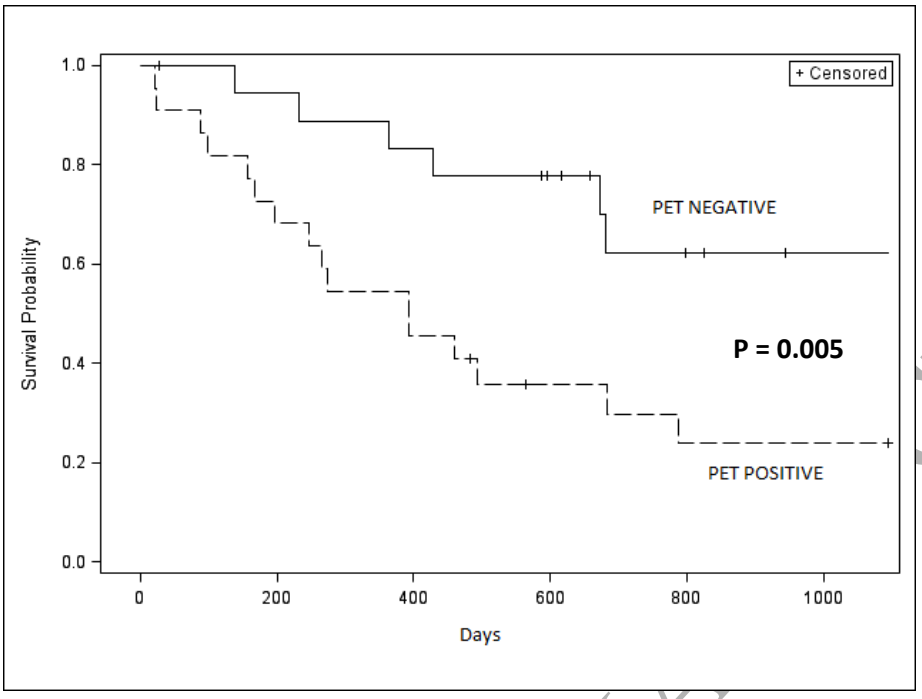


Figure 4: Kaplan-Meier estimates a) overall survival b) progression free survival c) GRFS relapse accordingly to pre-transplant FDG-PET status (positive if Deauville score ≥ 4)

a) overall survival accordingly to pre-transplant PET status



b) progression free survival accordingly to pre-transplant PET status



c) GRFS relapse accordingly to pre-transplant PET status

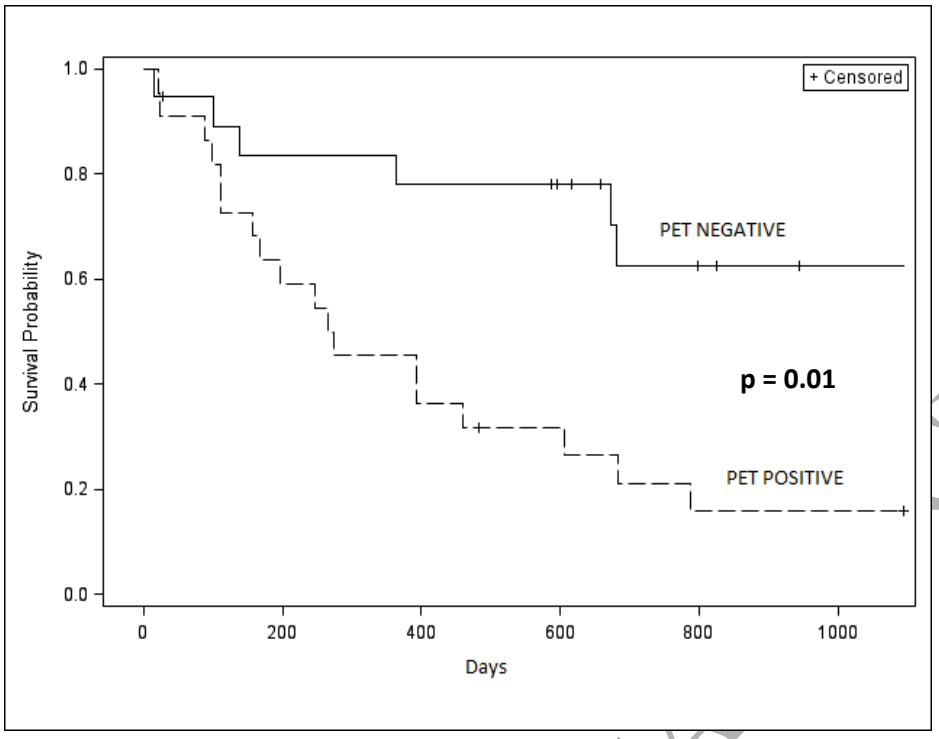


Table 1. Demographic, treatment and clinic characteristics of the 41 patients who received NMA haplo alloSCT. Data are expressed as medians (1st-3rd quartiles) or absolute frequencies (percentage).

	All patients
N.	41
Median Age, years	34 (25.7-37.0)
Gender (Male)	25 (60.9)
Donor/receiving mismatch	19 (46.0)
Mismatch with female donor	12 (29.2)
Response to the first therapy lines	
Refractory	30 (73.1)
Relapsed	11 (27.9)
ASCT	40 (97.5)
As bridge to allograft	5/40 (12.5)
As part of Salvage Chemotherapy	35/40 (87.5)
Median time to ASCT failure (months)	4.5 (0-8.8)
Brentuximab (SGN35)	22 (53.6)
Previous radiotherapy	26 (63.4)
Median number of therapy lines	4 (4-6)
Time from diagnosis to alloSCT (months)	34.6 (22.8-60.8)
CMV serostatus	
pos/pos	22 (53.7)
neg/pos	7 (17.1)
neg/neg	4 (9.7)
pos/neg	8 (19.5)
TOTAL CELLS*10^8	3.6 (2.6-4.1)
CD34+*10^6	3.9 (3.2-5.7)
CD3+*10^6	35.3 (25.1-46.9)
HCT–CI ≥ 3	8 (19.5)
Pre-allo FDG-PET positive (Five-point Deauville scale ≥4)	22 (53.7)
Engraftment	40 (97.5)

ASCT: autologous stem cell transplantation; HCT-CI: Hematopoietic Cell Transplantation Comorbidity Index; FDG-PET: Positron emission tomography

Table 2. Demographic, treatment clinic and characteristics among patients who underwent positron emission tomography (FDG-PET). The FDG-PET was considered positive when Five-point Deauville scale was ≥ 4. Data are expressed as medians (1st-3rd quartiles) or absolute frequencies (percentage).

	FDG-PET Positive	**FDG-PET Negative**	p-value
N	22	19	
Median Age, years	31.1 (26.1-36.2)	30.5 (25.8-39.5)	0.948
Gender (Male)	14 (63.6)	11 (36.4)	0.707
Gender Match	8 (36.4)	13 (68.4)	0.04
Response to the first therapy lines			0.138
Refractory	14 (63.6)	16 (84.2)	
Relapse	8 (36.4)	3 (15.8)	
autoSCT			1.0§
As bridge to Allo ASCT	1 (4.8)	1 (5.3)	
As part of Salvage Chemiotherapy	20 (95.2)	18 (94.7)	
Median time to autoSCT failure (months)	5.0 (0-10.2)	0.0 (0.0-8.2)	0.237
Brentuximab (SGN35)	9 (40.9)	13 (68.4)	0.078
Previous radiotherapy	15 (68.2)	11 (57.9)	0.495
Median number of therapy lines	4 (3-5)	4 (4-6)	0.484
Time from diagnosis to transplant (months)	33.9 (23.4-62.6)	33.1 (21.0-54.4)	0.509
CELLS*10^8	3.6 (3.0-4.2)	3.3 (2.2-4.1)	0.216
CD34*10^6	4.2 (3.2-5.7)	3.5 (3.0-5.9)	0.938
cd3*10^6	35.3 (26.8-49.3)	33.9 (24.5-49.0)	0.650

§ Fisher 's Exact Test; autoSCT: autologous stem cell transplantation; FDG-PET: Positron emission tomography

Table 3. Univariate and multivariate Cox analysis for overall survival, non-relapse mortality, relapse rate, progression free survival and graft-relapse free survival accordingly to pre-transplant variables

Table 3. Univariate and multivariate Cox analysis for overall survival, non-relapse mortality, relapse rate, progression free survival and graft-relapse free survival accordingly to pre-transplant variables

Variable	3-year OS HR (95%CI)		3-year NRM HR (95%CI)		3-year Relapse Rate HR (95%CI)		3-year PFS HR (95%CI)		3-year GRFS HR (95%CI)	
	Univ.	Cox	Univ.	Cox	Univ.	Cox	Univ.	Cox	Univ.	Cox
Pre-transplant FDG -PET (Deauville ≥ 4 vs < 4)	2.0 (0.5-7.8) p=0.31		0.6 (0.1-7.0) p=0.70		3.9 (1.4-10.7) **p=0.01**	4.4 (1.6-12.4) **p=0.005**	2.7 (1.1-6.7) **p=0.03**	3.8 (1.5-9.7) **p=0.005**	3.2 (1.3-7.7) p=0.01	3.2 (1.3-7.9) **p=0.01**
Response to the first therapy lines (Refractory vs responders)	0.9 (0.2-3.5) p=0.89		0.8 (0.1-9.3) p=0.89		1.2 (0.4-3.2) p=0.75		1.2 (0.5-3.1) p=0.67		1.5 (0.6-3.8) p=0.37	
Time from ASCT to relapse (≤ 6 months vs > 6 months)	0.6 (0.2-2.2) p=0.42		0.4 (0.04-4.8) p=0.49		1.1 (0.4-2.8) p=0.84		1.0 (0.4-2.4) p=0.99		1.2 (0.5-2.8) p=0.68	
Number of pre-transplant therapy lines (continuous)	1.7 (1.1-2.4) **p=0.01**	1.3 (0.8-2.0) p=0.23	2.7 (0.9-7.8) p=0.07		1.3 (1.0-1.8) p=0.09		1.4 (1.0-1.9) **p=0.03**	1.3 (1.0-1.8) p=0.06	1.2 (0.9-1.7) p=0.12	
Age (continuous)	1.0 (0.9-1.1) p=0.98		1.0 (0.9-1.1) p=0.59		1.0 (1.0-1.0) p=0.85		1.4 (1.0-1.9) **p=0.03**	1.0 (1.0-1.1) p=0.60	1.0 (1.0-1.0) p=0.55	
HCT-CI (≥ 3 vs < 3)	7.7 (2.2-27.2) **p=0.002**	5.0 (1.1-21.8) **p=0.03**	17.6 (1.4-221.0) **p=0.03**		2.8 (1.1-7.3) **p=0.04**	3.5 (1.3-9.3) **p=0.01**	4.0 (1.7-9.7) **p=0.002**	3.3 (1.2-9.0) **p=0.02**	4.2 (1.8-9.8) **p=0.001**	4.2 (1.7-9.9) **p=0.001**
Donor-receiving sex mismatch (F/M vs other combination)	1.3 (0.3-6.3) p=0.72		4.3 (0.3-69.8) P=0.31		0.7 (0.2-2.4) p=0.57		1.0 (0.3-3.0) p=0.99		0.8 (0.3-2.5) p=0.77	
Tumor burden (stage IIB-IV vs I-IIA)	1.9 (0.2-15.1) p=0.55		1.1 (0.1-16.7) p=0.94		17.2 (0.9-328.9) p=0.99		6.5 (0.9-49.4) p=0.07		7.8 (1.0-59.0) p=0.05	

OS: Overall Survival; NRM: non-relapse mortality; PFS: Progression free survival; GRFS: Graft relapse free survival

Table 4. Outcomes accordingly to pre-transplant FDG-PET status (positive if Deauville ≥ 4)

Pre-transplant PET status (n of pts)	n of pts relapsed (%)	3 year Relapse Rate	Grade II-IV aGvHD	3 year cGvHD	3 year PFS	3 year OS	3 year GRFS
Positive (22)	15/22 (68)	72.7%	0.0%	12.3%	27.3%	68.2%	18.2%
Negative (19)	5/19 (26)	33.9%	5.3%	10.5%	63.2%	84.2%	63.2%
p-value		**0.01**	0.86	0.79	**0.02**	0.31	**0.01**

FDG-PET: Positron emission tomography