Wednesday, March 29th

11:00-12:30

Oral 18: Chronic leukemia and MDS

Haplo-identical transplantation (haplo-HSCT) in patients with myelodysplastic syndrome (MDS): a report from the European Society of Blood and Marrow Transplantation

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Abstract

Background: The only curative treatment in patients with intermediate or high-risk MDS is allogeneic hematopoietic stem cell transplantation (HSCT) usually resulting in disease-free survival between 30 and 50% at long-term depending from the disease risk and the type of donor. The use of HLA mismatched unrelated donor (marrow, peripheral blood or umbilical cord blood) usually gives worse results than HLA-matched sibling or unrelated donor (Blood 2013 Saber, BBMT 2015 Robin). Family haplo-identical in patients with MDS is also an alternative option. The present study reports the European activity for haplo-identical transplantation in MDS patients. Method: All consecutive patients with a primary diagnosis of MDS transplanted from an HLA-mismatched related donor from 2007 to 2014 were included in this study if they had HLA and diagnosis information. Data were analyzed using multivariable Cox proportional hazards and cause-specific hazards models. Missing data were handled through multiple imputations by chained equations methods. Results: 230 patients were identified in the European registry Promise. Median age at transplant was 56 years (IQR: 46-64). WHO at time of transplant were RCMD in 31 (13.5%), RA/RARS/del5q in 12 (5.2%), RAEB-1 in 36 (15.7%), RAEB-2 in 67 (29.1%) and MDS transformed in AML in 84 (36.6%). Marrow blast were < 5% in 72.2% at time of transplant. 181 (78.7%) patients had 2 or more HLA mismatches with the donor while other patients had only one HLA-mismatch (21.3%). 117 (51.5) patients received a reduced intensity (RIC) regimen and 62 (27.3%) received a total body irradiation. In vivo T-cell depletion was performed in 105 (46.1%) patients while ex-vivo T-cell depletion was performed in 34 (14.9%) patients. GvHD prophylaxis was based on post-transplant cyclophosphamide (PTC) in 102 (44.7%) patients; 3-year overall survival (OS), disease-free survival (DFS) were 32% (95%CI: 26-41%) and 29% (95%CI: 23-37), respectively. Cumulative incidence of 3-year non-relapse mortality (NRM), grade II-IV acute GVHD and chronic GVHD were: 49% (95%CI: 41-56), 31% (95%CI: 25-38) and 30% (95%CI: 23-36), respectively. Regarding only patients treated by PTC, 3-year OS, DFS and NRM were 38%, 34% and 41%. NRM was particularly high in patients having received a myeloablative conditioning (MAC) regimen as (59% vs 40%). The best outcome were observed in patients with a WHO diagnosis with less than 5% marrow blasts (OS: 60%, DFS: 51%, NRM: 34%). Multivariable analyses showed that the following risk factors impacted OS, DFS, and NRM: transformation into AML, not in CR at time of transplant, a female donor for a male recipient, myeloablative conditioning regimen and the absence of PTC (see Table below).

<table>
<thead>
<tr>
<th></th>
<th>DFS</th>
<th>OS</th>
<th>NRM</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hazard ratio</td>
<td>p-value</td>
<td>Hazard ratio</td>
</tr>
<tr>
<td>Transformation in AML</td>
<td>1.84</td>
<td>0.033</td>
<td>2.19</td>
</tr>
<tr>
<td>Non CR at time of</td>
<td>1.93</td>
<td>0.001</td>
<td>1.90</td>
</tr>
<tr>
<td>transplant</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>--------------------------------</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Female donor for male recipient</td>
<td>1.53</td>
<td>0.062</td>
<td>1.67</td>
</tr>
<tr>
<td>MAC</td>
<td>1.47</td>
<td>0.048</td>
<td>1.56</td>
</tr>
<tr>
<td>PTC</td>
<td>0.49</td>
<td>0.038</td>
<td>0.44</td>
</tr>
</tbody>
</table>

Conclusions: DFS in patients transplanted from an haplo-identical donor is close to outcome reported in HLA-mismatched donor other than haplo. Results have been improved by PCT which was associated with a significant better DFS and OS. Nevertheless, NRM remains relatively high at 41% after PCT.

**Disclosure of conflict of interest**

No
Long-term Survival of Patients with MDS after Allogeneic Transplantation: A report from the Chronic Malignancies Working Party of EBMT

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Abstract

Introduction: The median age at diagnosis of Myelodysplastic Syndromes (MDS) is 76 years. The incidence of MDS increases with increasing age and men have a higher incidence than women. Currently, allogeneic hematopoietic stem cell transplantation (HCT) is the only curative treatment option for patients with MDS. When interpreting outcomes after HCT the age- and sex-specific life expectancy has to be considered. Therefore, we studied excess mortality after HCT in comparison to an age-, sex-, country- and calendar year-matched general population in various time periods after HCT for different age cohorts. Patients and Methods: Data from adult patients with MDS who had received a first allogeneic HCT between January 2000 and December 2012, and who were registered with the EBMT database, were analyzed. Patients who received mismatched related HCT, cord-blood transplantation and patients with more than 20% marrow blasts at any time during their history were excluded from the analysis. Survival probabilities were calculated by means of the Kaplan-Meier estimator. Excess mortality compared to an age-, sex-, country- and calendar year-matched general population was estimated by relative survival methods. Results: In total 3813 patients were included into the analysis. The median follow-up of patients alive at the end of follow-up was 49 months. The number of transplants increased from 56 in year 2000 to 660 in 2012. Median age at HCT increased from 47 (range 18 to 66) to 57 years (18-74). 60% of patients were male. 39% of the patients had an HLA-matched sibling donor and 58% received reduced-intensity conditioning. For the whole cohort of patients, the overall survival (OS) was 46% (95%-CI: 45-48%) at 5 years and 40% (95%-CI: 37-42%) at 10 years. For patients <55 years or ≥55 years at the time of HCT 10-year OS probabilities were 48% (95%-CI: 45-51%) and 31% (95%-CI: 28-34%) and for patients with or without excess blasts (EB) at HCT the 10-year OS probabilities were 33% (95%-CI: 30-37%) and 46% (95%-CI: 43-49), respectively. The probability to be alive event-free at 2 years after HCT was 52% (95%-CI: 50-54%). In the population who reached this landmark, the probabilities to be alive at 10 years after HCT were 82% (95%-CI: 78-86%) and 65% (95%-CI: 59-72%) for patients <55 years or ≥55 years at HCT and 68% (95%-CI: 62-74%) and 81% (95%-CI: 77-85%) for patients with or without EB at HCT. For patients below the age of 45 at HCT who survived the first two years after HCT event-free, the probability to be alive 5 years later was 91% (95%-CI: 86-96%) for men compared to 99% survival chance in the matched general population and 94% (95%-CI: 90-97%) for women compared to 99.5%. For patients 65 years or older at HCT, these numbers were 70% (95%-CI: 58-85%) and 88% for men and 65% (95%-CI: 49-86%) and 93% for women. Conclusion: Long-term
follow-up data derived from the EBMT registry show that patients experience excess mortality compared to the general population, also beyond the 2-years landmark. However, especially for older male patients, the risk of dying from causes also relevant for an age-matched population was substantial. For elderly patients this background mortality should be considered when interpreting results after HCT. The results also indicate that a significant fraction of patients can be cured by HCT.

**Disclosure of conflict of interest**

No conflict of interest
Fludarabine/Treosulfan is a promising condition for MDS/CMML-patients. A retrospective single center study.

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Abstract

Background: Allogeneic haematopoietic cell transplantation (HCT) of MDS/CMML is still a challenge with a disease free survival (DFS) between 35 - 40%, transplant related mortality (TRM) between 15-20% and relapse rates (RR) between 20-30 %. However, improved results with Fludarabine and Treosulfan conditioning has been published 1,2. Therefore, we have implemented this regimen at our center and now the first results are presented and compared with former transplantation data. Method/Patients: A retrospective single center study of 164 patients with MDS (n=148) and CMML (n=16), who underwent allogeneic HCT between 1. Jan 2000 – 31. Oct 2016 at Copenhagen University Hospital. From 2000-2014, a non-myeloablative conditioning (NMA) with Fludarabine 90 mg/m2 + TBI 2 Gy was used for patients > 50 years. A myeloablative conditioning (MAC) with cyclophosphamide 120mg/kg + TBI 12 Gy was used for patients ≤ 50 years. From September 2014 the reduced toxicity conditioning (RTC) Fludarabine 150 mg/m2 + Treosulfan 42 g/m2 has been implemented for patients ≤ 65 years. Patients > 65 years are still treated with NMA. Immunosuppression: NMA: Tacrolimus and MMF, MAC: Cyclosporin and MTX and Flu/Treo: Tacrolimus and MTX. ATG has not been added for matched unrelated donors (MUD).

<table>
<thead>
<tr>
<th>Regimen</th>
<th>NMA (Flu-TBI 2 Gy)</th>
<th>MAC (Cy-TBI 12 Gy)</th>
<th>Flu/Treo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (n = 164)</td>
<td>95 pt</td>
<td>38 pt</td>
<td>31 pt</td>
</tr>
<tr>
<td>Median age, years</td>
<td>61 (range 37-75)</td>
<td>38 (range 13-59)</td>
<td>60 (range 28-66)</td>
</tr>
<tr>
<td>CMML</td>
<td>9 pt (9 %)</td>
<td>3 pt (8%)</td>
<td>4 pt (13 %)</td>
</tr>
<tr>
<td>Stem cell source</td>
<td>PB: 98 % BM: 0% UCB: 2 %</td>
<td>PB: 50 % BM: 50 %</td>
<td>PB: 100 %</td>
</tr>
<tr>
<td>Donor MUD/SIB</td>
<td>70%/30 %</td>
<td>61%/39 %</td>
<td>74%/26%</td>
</tr>
<tr>
<td>More than 5% blast at time of HCT</td>
<td>6 pt (6 %)</td>
<td>11 pt (28 %)</td>
<td>9 pt (29 %)</td>
</tr>
</tbody>
</table>

Results: The years overall survival (OS) for Flu/Treo (2): 86 % (CI: 65-94). For NMA (0): 60% (CI: 49-69) and MAC (1): 55% (CI: 38-69). The median follow up time were: Flu/Treo: 1,2 years; NMA: 4,7 years and MAC: 7,2 years. A significant difference in OS in favor of Flu/Treo was found when compared to MAC (p =0,023), NMA (p = 0,047) and both groups (p = 0,032). No difference in OS between MAC and NMA (Fig 1) was found. Two patients treated with Flu/Treo have relapsed corresponding to a cumulative incidence of relapse (CIR) after 2 years of 0,088 (CI: 0,014-0,251). CIR for NMA: 0,237 (CI: 0,156-0,328) and MAC: 0,184 (CI: 0,080-0,323). TRM after 2 years: Flu/Treo: 0,150 (CI: 0,044-0,315); NMA: 0,196 (CI: 0,122-0,284) and MAC: 0,316 (CI: 0,175-0,467). Acute GvHd (grade 1-4) rate was comparable for Flu/Treo and NMA (0,24(CI: 0,10-0,40) vs 0,26(CI: 0,18-0,36 ))) and reduced compared to MAC ( 0,55(CI: 0,38-0,70)). Conclusion: Fludarabine/Treosulfan is a promising conditioning regimen for MDS/CMML pts. Two years OS was significantly improved compared to standard MAC and NMA, which may be explained by a lower relapse rate without a corresponding increase in TRM.
References


Disclosure of conflict of interest

None
Ibrutinib for bridging to allogeneic hematopoietic stem cell transplantation (alloHCT) in chronic lymphocytic leukemia (CLL) and mantle cell lymphoma (MCL) is safe and effective: Updated results of a study by the EBMT Chronic Malignancy and Lymphoma Working Parties, the French Cooperative Group for CLL, and the Société Française de Greffe de Moelle et de Thérapie Cellulaire (SFGM-TC)

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Abstract

BACKGROUND: The advent of the B cell receptor inhibitor (BCRI) ibrutinib has improved the outlook of patients with CLL and MCL failing chemoimmunotherapy (CIT). However, the impact of ibrutinib on the feasibility and safety of a subsequent alloHCT is unknown. Here we present updated results of an EBMT survey on the outcome of alloHCT following prior exposure to ibrutinib in patients with CLL or lymphoma (EBMT study code LWP 2013-N-03/CMWP 44204425). DESIGN: Eligible were patients aged >18 years registered with the EBMT data office for a planned alloHCT for CLL or lymphoma after pre-exposure to ibrutinib at any time before transplant. Baseline patient, disease, and transplant data was collected from MED-A forms. Centers were requested to provide additional treatment and follow-up information. RESULTS: As of Dec 2, 2016, 63 patients (76% male) were included. Diagnosis was CLL in 43 patients, MCL in 17 patients, and other lymphoma in 3 patients. The median age at HCT was 56 (38-72) years and the median number of treatment lines prior to ibrutinib 2 (1-9). 80% of the patients with lymphoma but none of the CLL patients had a prior autoHCT. Patients had been on ibrutinib for a median of 187 (11-671) days. In 3 patients, ibrutinib had been stopped because of disease progression >120d before transplant, whereas the interval between ibrutinib withdrawal and alloHCT was 15-120d in 39%, 4-14d in 42%, and 0-1d in 14% of the patients. Of the CLL patients, 37% had a TP53 lesion, and 87% and 65% met at least one of the 2007 and 2014 EBMT criteria for high-risk CLL, respectively. Disease status at alloHCT was sensitive in 81% of the CLL patients, and in 89% of the patients with lymphoma. The median time to reach neutrophils of >0.5/nl and platelets of >20/nl was 17 (6-68) and 14 (5-46) d post transplant, respectively. Acute GVHD grade 2-4 (3-4) was observed in 37% (7%) of 58 evaluable patients, and overall and extensive chronic GVHD occurred in 41% and 24% of 46 patients at risk. With a median observation time of survivors of 7 (1-29) months, there were only 3 non-relapse deaths, translating into a 1-year non-relapse mortality (NRM) of 9%. 1-year relapse incidence (REL), progression-free survival (PFS), and overall survival (OS) was 36%, 58%, and 73% for CLL, and 36%, 59%, and 70% for MCL. 2-year OS from start of ibrutinib was 78% for CLL and 74% for MCL. In the 40 evaluable patients with CLL, sensitive compared to refractory disease status at alloHCT was associated with significantly better REL and EFS. In 31 CLL patients transplanted while still responding to BCRI, 1-year REL, EFS and OS were 28%, 63% and 80%, respectively. In these 31 patients, not counting relapse events that could be successfully retreated with ibrutinib, 1-year ibrutinib-sensitive survival was 73%. TP53 status, duration of ibrutinib exposure, interval between ibrutinib withdrawal and alloHCT, and type of conditioning had no impact on REL. CONCLUSIONS: Ibrutinib for bridging to alloHCT
for CLL and MCL does not appear to adversely affect engraftment, GVHD risk, and NRM. Given the relatively good outlook of patients who undergo alloHCT while still responding to ibrutinib, this drug appears to be capable of making patients with otherwise refractory CLL transplant-eligible. Moreover, this preliminary data does not suggest short-term inferiority of switching from ibrutinib to HCT (compared to continuing ibrutinib without HCT) for patients with BCRi-sensitive CLL.

Disclosure of conflict of interest

PD: Janssen - Advisory Board
Bridging with Idelalisib appears safe in patients with chronic lymphocytic leukemia (CLL) prior to allogeneic hematopoietic stem cell transplantation (alloHCT): A Report from the EBMT Chronic Malignancies Working Party

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Abstract

BACKGROUND: In future, many patients with high-risk CLL will be intolerant or refractory to the BTK-inhibitor ibrutinib when they are referred for allogeneic hematopoietic cell transplantation (alloHCT). The phosphatidylinositol 3-kinase (PI3Kδ)-inhibitor, idelalisib, is active also in ibrutinib-refractory CLL. The PI3-kinase exerts pleiotropic effects on cell metabolism, migration, proliferation, survival, and differentiation in lymphoid tissues. Autoimmune-mediated side effects such as colitis, hepatitis, and pneumonitis have been reported on treatment with idelalisib. Exposure to idelalisib could thus interfere with subsequent alloHCT. Therefore, we analyzed the outcome of patients with CLL who had received idelalisib prior to alloHCT.

METHODS: Patients were eligible if registered with the EBMT data office for a planned alloHCT for CLL after exposure to idelalisib at any time before transplantation. Minimal essential transplant data were collected on standard forms. Centres were requested to provide information on idelalisib treatment and follow-up.

RESULTS: As of Dec 2, 2016, 32 patients with CLL (63% male) had received alloHCT after exposure to idelalisib in 2015 or 2016. Median age at alloHCT was 57 (36-67) years. 44% of patients had CLL with deletion 17p and/or deletion 11q. Almost all patients (96%) had a Karnofsky Performance Status of 80% or higher. The median number of treatment lines prior to alloHCT was 3 (1-7), including treatment with ibrutinib in six patients (19%). Idelalisib plus Rituximab was the last regimen prior to alloHCT in 29 patients (91%). Complete remissions and partial remissions were reported for 10% and 75% of patients. Reduced intensity and myeloablative conditioning was administered in 78% and 22% of patients. Anti-thymocyte globulin was given to 63% of patients and alemtuzumab to 28% of patients. Donors were HLA-identicalsiblings for 44% of patients, mismatched related donors for 16% of patients and unrelated volunteers for the remaining patients. One patient each received cord blood or a bone marrow while the remaining graft sources were peripheral blood stem cells. No primary graft failure and one secondary graft failure were reported. The median time to neutrophils of >0.5/μl and platelets of >20/μl was 19 days (11-40) and 15 days (8-50) after alloHCT, respectively. Acute GVHD grade 2-4 was observed in 44% of evaluable patients, and overall chronic GVHD in 25% of patients at risk. Twenty-six patients were alive after a median observation time of 4 (0-19) months after alloHCT. Four patients experienced relapse or progression and five patients succumbed from complications after alloHCT. This translated into 6-month cumulative incidences of 7% and 10% for non-relapse mortality (NRM) and relapse/progression. The probability of 6-month progression-free and overall survival was 83%.
(95%-CI, 68% to 100%) for both endpoints. Notably, of those 6 patients who had been exposed to ibrutinib and idelalisib two patients have relapsed and two patients have died from complications. CONCLUSIONS: This report shows that idelalisib-based salvage therapy can successfully bridge patients with CLL to alloHCT. Adverse safety signals with respect to engraftment, acute GVHD and early mortality could not be identified. Longer follow-up is needed in order to assess disease-control after alloHCT in this ultra high-risk patient population. Updated outcomes will be presented at the annual meeting.

Disclosure of conflict of interest

No conflict of interest
Allogeneic Stem Cell Transplantation versus B-Cell-Receptor Inhibitors in 17p Deletion and/or Refractory Chronic Lymphocytic Leukemia: a Retrospective Comparative Analysis of ‘Real Life’ Approaches to High Risk Patients.

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Abstract

Allogeneic stem cell transplantation (alloSCT) has been indicated in chronic lymphocytic leukemia (CLL) with 17p deletion (del) and/or in CLL patients who experience early relapse or not responding to chemoimmunotherapy. Recently, B-cell receptor inhibitors (BCRI) have shown high efficacy with a low toxicity, making the choice of an alloSCT challenging even in high risk patients. The aim of the study is to highlight the outcome of different clinical approaches available in the era of the new drugs in high risk CLL patients. This is a multicenter retrospective analysis on 88 patients treated in 8 Italian Centers. Inclusion criteria were: i) age ≤ 70 years; ii) responding to one of the EBMT criteria for elegibility to alloSCT in CLL; iii) alloSCT from 2001. Patients who received BCRI before alloSCT or ineligible to alloSCT due to comorbidities were excluded. Patients were assigned to alloSCT or BCRI based on physician and/or patient choice or unavailability of a donor. The analysis started from transplant date or start date of BCRI therapy. Fifty patients (M/F: 42/8) received an alloSCT, and 38 (M/F 30/8) were treated with BCRI (ibrutinib n=28, rituximab-idelalisib n=10). Median age was 55 (range, 34-68) in alloSCT and 60 years (42-69) in BCRI (p=0.06). FISH data were available in 34/50 (68%) alloSCT patients: 17p del was positive in 21 (62%) (de novo n=12, acquired n=8, unknown n=1). Elegibility criteria for alloSCT group were: early relapse n=11, refractory n=7, ASC relapse n=11, 17p del n=21. FISH data were available in all BCRI patients: 17p del was positive in 26 (68%) (de novo n=8, acquired n=14, unknown n=4). Elegibility criteria for BCRI group were: early relapse n=2, refractory n=9, ASC relapse n=1, 17p del n=26. AlloSCT group had more patients in early relapse or with a failed ASCT (p=0.03 and p=0.01). Heavy chain gene rearrangement was available in 26/50 (52%) alloSCT and 35/38 (92%) BCRI patients and was unmutated in 87% and 86%, respectively. The median number of previous therapy was 2 in both groups (alloSCT: range 1-7; BCRI: range 0-8, p=0.25). Reduced-intensity conditioning regimen was used in 48/50 alloSCT patients, and donor type was sibling in 19, matched unrelated in 26 and haploidentical in 5 cases. Disease status before alloSCT was complete remission (CR)=20, partial remission (PR)=17, stable/progressive disease (SD/PD)=13. The median follow-up was 33 months (1-134) and 14 months (3-32), respectively for alloSCT and BCRI group (p=0.0008). Two-year OS was 59% vs 79% in alloSCT and BCRI, respectively (p=0.32). The cumulative incidence of relapse at 2 years was 30% in alloSCT and 23% in BCRI, with a non-relapse mortality of 20% after alloSCT. Median PFS was 18.6 months (range 1-134) and 12.6 (range 3-24.6) in alloSCT and BCRI, respectively. Two-year PFS was 54% in alloSCT and 77% in BCRI (p=0.19). The main cause of treatment failure was disease progression. These preliminary retrospective data showed that so far no significant difference in the outcome of 17p del and/or refractory CLL patients have been observed after either alloSCT or BCRI inhibitors. The significant different follow-up of the two groups implies some limits: i) BCRI inhibitors still have to show long term responses; ii) alloSCT results may improve over the next future by a better selection of patients and the improvement of the transplant procedures. The combination of the two strategies will increase the chance of cure of poor risk CLL patients.
Disclosure of conflict of interest

No disclosure
AN EBMT PROSPECTIVE NON-INTERVENTIONAL STUDY OF OUTCOMES AND TOXICITY OF ALLOGENEIC STEM CELL TRANSPLANTATION IN CHRONIC MYELOID LEUKEMIA PATIENTS PREVIOUSLY TREATED WITH SECOND GENERATION TYROSINE KINASE INHIBITORS

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Abstract

Introduction: Allogeneic stem cell transplantation (SCT) remains a treatment option for patients with chronic myeloid leukemia (CML) that fail to respond to tyrosine kinase inhibitors (TKI). While the use of Imatinib seems to have no adverse impact on outcomes after transplant, little is known on the effects of prior use of second generation TKI (2GTKI). We present the results of a prospective non-interventional study (NIS) performed by the EBMT of 383 consecutive allogeneic SCT in patients diagnosed with CML from 2009 to 2013. Results: Median follow-up was 37 months (1-77). The median age was 45 years (18-68) and 251 (65%) were males. Disease status at the start of 2GTKI was: First chronic phase - CP1 (123, 46%), Accelerated phase or >CP1 (67, 25%) and blast crisis (75, 28%). The choice of 2GTKI was: Dasatinib (155, 40%), Nilotinib (64, 17%) and a sequential combination of Dasatinib/Nilotinib with or without Bosutinib/Ponatinib (164, 43%). Of note, 29% of patients that received Dasatinib were in CP1 at the start of 2GTKI and at the time of SCT compared with 45% at the start and 40% at SCT for patients treated with Nilotinib. Overall disease status at SCT was CP1 in 139 patients (38%), AP in 163 (45%) and BC in 59 (16%). The median interval from diagnosis to SCT was 22 months (2 – 267) and the median interval between starting 2GTKI and SCT was 10 months (1 – 191). The donor was an HLA identical sibling in 130 cases (35%) and unrelated in 244 (65%). The majority of SCT were performed using PBSC (295, 77%), while 272 (71%) were myeloablative and 111 (29%) reduced intensity conditioning. The EBMT score was low (0-2) in 26 (7%), intermediate (3-4) in 216 (62%) and high (5-7) in 107 (31%). Primary graft failure (PGF) occurred in 10 (3%) cases, while the incidence of acute GVHD was 34% (95% CI 29-39) and chronic GVHD (CGVHD) was 60% at 5 years (95% CI 54-66). CGVHD occurred at a median of 5.7 months (3-61) post SCT. Other post SCT complications included veno-occlusive disease of the liver (VOD) in 6 cases (2%) and severe infection in 195 (65%). There were no differences in post-transplant complications amongst the 3 different 2GTKI subgroups. Overall non-relapse mortality was 18% (95% CI 14-22) at 12 months and 24% (95% CI 19-29) at 5 years. Relapse incidence was 36% (95% CI 29-42), overall survival was 56% (95% CI 50-62) and relapse-free survival was 40% (95% CI 33-47) at 5 years. Overall survival was 67% (95% CI 59-75) at 5 years for patients in CP1. No differences in post-transplant outcomes were found amongst the 3 different 2GTKI subgroups. However, the EBMT score, performance status and disease stage at 2GTKI and at SCT were predictive of overall and progression-free survival. Discussion: This prospective study demonstrates the feasibility of allogeneic SCT in patients previously treated with 2GTKI. The rate of post-transplant complications seems comparable to that of patients treated with imatinib or TKI-naïve. We observed no differences between outcomes for patients receiving Dasatinib, Nilotinib or any other combination of 2GTKI (including Bosutinib and Ponatinib) pre-SCT. However, patients receiving Dasatinib were more likely to proceed to SCT in advanced phase than in CP1. Patients in CP1 have a very good overall survival despite prior treatment with 2GTKI. Of note, even after 2GTKI, the EBMT score remains a strong predictor of overall and disease-free survival for CML patients undergoing allogeneic SCT.
Disclosure of conflict of interest

None
Salvage Use of Ibrutinib after allogeneic hematopoietic stem cell transplantation (allo-HSCT) for B cell malignancies: A study of the French Cooperative Group for CLL, the Société Française de Greffe de Moelle et de Thérapie Cellulaire (SFGM-TC), and the European Society for Blood and Marrow Transplantation (EBMT)

Chronic Malignancy and Lymphoma Working Parties

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Abstract

BACKGROUND: Allo-HSCT is an accepted treatment option for patients with relapsed and refractory mantle cell lymphoma (MCL) or high-risk chronic lymphocytic leukemia (CLL). This treatment option is currently reshaped by the introduction of pathway inhibitors (PWI). In case of disease relapse after transplantation, the outcome is a major concern and the prognosis is dismal. PWI could be very promising when used before and/or after transplantation. The purpose of our study is to provide information on the safety and efficacy of ibrutinib when administered after allo-HSCT for CLL or MCL. DESIGN: This study included adult CLL or MCL patients registered with the EBMT for an allo-HSCT and who received ibrutinib after transplant. Baseline patient, disease, and transplant data were collected from MED-A forms. Centers were requested to provide additional treatment and follow-up information. RESULTS: A total of 60 patients, 40 (67%) males, transplanted between September 2002 and December 2015 were included. Diagnosis was CLL in 55 (92%) patients and MCL in 5 patients. Median age at transplantation was 55 (range: 38-66) years and the median number of treatment lines prior to transplantation was 3 (1-10). Before transplantation, in CLL patients, del17p was present in 17/55 (31%) of cases and del11q was present in 10/55 (18%) other cases. Prior to allo-HSCT, 5 patients (2 CLL and 3 MCL) had received an auto-HSCT and 6 other CLL patients had been exposed to ibrutinib for a median of 236 (190-285) days. Disease response at allo-HSCT was sensitive in 45/60 (75%) patients. Conditioning was reduced-intensity in 41/60 (68%) patients and included in-vivo T cell depletion in the majority of cases (29/41). Donors were identical siblings in 21 (35%) patients, 55 (92%) had PBSC as stem cell source. Acute GVHD occurred in 14 patients (9 grade II, 5 grade III), while chronic GVHD occurred in 25 patients (13 limited, 12 extensive) but had resolved in 15/25 patients prior to ibrutinib. Patients received ibrutinib for relapse after allo-HSCT (median time from allo-HSCT to progression: 21 (0.5-81) months). Donor lymphocyte infusions (DLI) were administered in 26 patients, 4 among them were after ibrutinib start. Ibrutinib was generally well tolerated; major toxicities were secondary cancers in 2 patients (1 oesophageal and 1 gastric) and grade 4 toxic epidermiolysis in 1 patient. De novo limited chronic GVHD occurred in 1 patient while on ibrutinib. Overall, 42/60 (70%) patients had responsive disease after ibrutinib (20 reached CR, among them 5 with MRD-). Fourteen patients had discontinued ibrutinib, 4 because of toxicity (2 secondary cancers, 2 skin toxicity), and 10 because of disease progression. Overall, 16 patients relapsed (median PFS=24 months), 9 died (all CLL) only from disease progression. Two-years OS and PFS probabilities were 72% and 51% respectively. OS and PFS after ibrutinib were not influenced by del17p/del11q while patients with late relapse after allo-HSCT (>36 months) had a better OS (p=0.03) and PFS (p=0.06) after ibrutinib. At the last follow-up, 46 (77%) patients are still on ibrutinib after a median exposure of 407 (14-937) days and 31 patients have ongoing response (18 in CR). CONCLUSION: We showed in this largest series of patients described to date in this indication, that ibrutinib can be safely administered for CLL/MCL relapse after allo-HSCT, with an efficacy at least similar to non-transplanted patients with high-risk disease.
Disclosure of conflict of interest

None