

<b>Meeting title:</b>	Acute Leukemia Working Party Business Meeting
<b>WP/Others:</b>	ALWP

<b>Location:</b>	Milan, Italy	<b>Date:</b>	30/03/2014
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<b>Author:</b>	Sebastian Giebel
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<b>Participants:</b>	<b>EBMT:</b>	ALJURF Mahmoud; BARON Frédéric; BAZARBACHI Ali; BELLIDO Mar; BRUNE Mats; BRUNET Salut; BUG Gesine; CERRETTI Raffaella; CORRADO Girmenia; CRADDOCK Charles; CZERW Tomasz; EAPEN Mary; ESTEVE Jordi; FACCHINI Luca; FLOISAND Yngvar; GIEBEL Sebastian; GINDINA Tatiane; GORIN Norbert-Claude; GUIMARAES Jose Eduardo; HICHERI Yosr; IORI Anna Paola; LABOPIN Myriam; LIESTOL Sigurd; LUIS LOPEZ Jose; MAILHOL Audrey; MCDONALD Andrew; MIDDEKE Moritz; MOHTY Mohamad; NAGLER Arnon; OTTMANN Oliver; PASSWEG Jakob; PAVLU Jiri; PÉREZ REQUEJO Isabel; PIEMONTESE Simona; POIRE Xavier; POLGE Emmanuelle; RICHARDSON Deborah; RINGDEN Olle; ROTH GUEPIN Gabrielle; RUBIO Marie-thérèse; RUGGERI Annalisa; TORLEN Johan; VAN STEENWEGHEN Steven; VERSLUIS Jurjen; ZAREU Janette
	<b>Other:</b>	
<b>Apologies</b>		

<b>Distribution:</b>	EBMT members
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## MINUTES & record of decisions

**Introduction (ALWP Chair: M. Mohty; ALWP secretary: S. Giebel; ALWP statistician: M. Labopin)**

Prof. Mohamad Mohty presented major achievements of ALWP, which include (i) organization of high level accredited educational activities pertinent to acute leukemia (latest symposiums: Nantes in 2008, Barcelona in 2009, Milan in 2010, Warsaw in 2011, Milan in 2012, Marseille 2013); (ii) designing and support to prospective clinical trials in the field of acute leukemia across member centres; (iii) generation of high quality retrospective studies addressing different issues related to acute leukemia management and therapy.

Over the last 2 years, the activity of ALWP was reflected by over 20 scientific papers published in Journal of Clinical Oncology, Blood, Leukemia and other high quality journals. Results of the studies were presented at major congresses such as the EBMT and ASH meetings.

So far structure of ALWP includes 6 subcommittees: Autologous SCT (NC. Gorin), Immunotherapy (C. Schmid), Alternative donors (F. Ciceri), RIC allo-SCT (A. Nagler), Molecular markers (J. Esteve), and Developing centers (S. Giebel).

Prof. Mohamad Mohty has been elected a new president of the EBMT. Participants of the business meeting congratulated him wishing great success in the new role. They also expressed their gratitude for his enormous engagement in the activity of ALWP as well as creativity resulting in marked increase of the number of publications and educational events organized by the working party.

The ongoing election for a new ALWP chairman has been reminded. Prof. Arnon Nagler (Tel-Hashomer, Israel) and prof. Sebastian Giebel (Gliwice, Poland) were candidates, both accepted and recommended by members of the ALWP.

### Completed ALWP surveys

- TBI in current clinical practice (S. Giebel): The aim of the survey was to explore the diversity of TBI techniques across Europe. 56 centers from 23 countries responded to the questionnaire. The analysis revealed extreme heterogeneity across centers with regard to total dose of TBI, dose per fraction, dose rate, treatment unit and technique, dosimetry and organ shielding. The differences may influence both the efficacy and safety of the procedure, which requires further investigation. Optimization and standardization of TBI is the final goal. (oral presentation during the EBMT meeting, Epub in "Cancer").
- Chemotherapy dosing (A. Nagler): There is a lot of controversy regarding optimal dose calculation of drugs used in conditioning with regard to adjustment for body mass and body surface. The aim of the survey was to determine current practice in Europe. The analysis revealed major differences across centers and countries (oral presentation during the EBMT meeting, manuscript submitted).

### Various proposals/studies

#### Ongoing studies

- The impact of irradiation dose rate on the efficacy and safety of TBI-based myeloablative allogeneic HSCT for acute leukemia (S. Giebel). Center selection based on participants of TBI survey. The effect of dose rate will be analyzed among patients treated with TBI 12 Gy in 6 fractions for 3 days.
- Impact of ATG dose and timing on allo-SCT outcome (R. Devillier/ D. Blaise)
- Survey on the use of Thiotepa as part of the conditioning regimen in ALL and AML (S. Eder) (EBMT Poster)
- For male patients with ALL and AML, who is the best donor? (O. Ringden). The manuscript has been accepted in Transplantation..
- Allogeneic stem cell transplantation for patients older than 60 years with acute lymphoblastic leukemia (G. Roth). RIC-HSCT in this patient population has not been extensively studied. The study is feasible.
- Impact of previous gemtuzumab administration in AML patients after allo-SCT (G. Battipaglia).
- 2nd allogeneic transplant as rescue strategy for acute leukemia patients who relapse after an initial RIC allogeneic transplant (R. Vrhovac)

#### Proposals

- Impact of pre-existing invasive mould infections on transplant-related complications and survival after allo-SCT (O. Penack): Proposal of a joint study with acute Leukemia WP and IDWP
- Allogeneic hematopoietic stem cell transplantation for primary refractory acute lymphoblastic leukaemia. (J. Pavlu). A joint effort with the European Group for Adult ALL has been suggested to compare results of alloHSCT with other treatment options (conventional chemotherapy, bispecific antibodies)

- Allogeneic stem cell transplantation in adult acute leukemia patients with central nervous system involvement at diagnosis (K. Halaburda). Data on CNS-oriented treatment are difficult to obtain. The study would require additional data collection and not feasible immediately.

## Activity of the subcommittees:

### Immunotherapy (Leader: Dr. C. Schmid):

#### Ongoing studies

- Pre-emptive or prophylactic use of DLI (C. Schmid). Data collection is ongoing. All centers are welcome to participate in the study.
- Use of azacitidine after alloHCT for AML (C. Craddock). The study is supported by an unrestricted grant from Celgene. Data collection is on-going with the aim to submit an abstract to ASH 2014 meeting.
- Sequential Chemotherapy Followed by RIC allo-SCT in Adult Patients with Relapsed or Refractory AML (O. Ringden) Additional data on AML karyotype should be collected before final analysis.
- Long term results after second transplant for relapsed AML (G. Andreoli). Analysis has been performed. The manuscript is in preparation.
- Second allograft versus DLI in relapsed AML (M. Kharfan-Dabaja). Initial results have been presented as ASH 2013 Poster. Manuscript in preparation.
- Impact of CD3+ cell dose on outcome after RIC-alloHSCT for AML (T. Czerw). Initial analysis indicates the effect of CD3+ dose may be modulated by the use of ATG.

#### Proposals

- The GVL effect in HLA-identical siblings, MUD and haplo transplants using RIC as opposed to MAC (O. Ringden) Association of GVHD with relapse incidence would be analyzed according to the type of donor and intensity of conditioning. The number of haploHSCT may be insufficient; study to be considered at a later stage.
  - Revisiting the impact of ex-vivo T-cell depletion of PBSC on allo-SCT outcome in patients given myeloablative allo-SCT for AML in CR (F. Baron). Data on immunosuppression are needed. They may be collected by asking centers for their strategies. Hence, individual patient-oriented queries are not necessary and the study is feasible.
  - Determinants of the kinetics of disease relapse after an allograft for AML (C. Craddock).
  - Impact of disease, preparative regimen and immunological factors on timing of relapse after allogeneic stem cell transplantation in AML (M. Yesherun). Characteristics of patients experiencing early versus late relapses is planned.
- ➔ The above mentioned proposals from C. Craddock and M. Yesherun should be merged.

### Developing centers (Leader: Dr. S. Giebel):

#### Ongoing studies

- Impact of socio-economic factors on non-relapse mortality after alloHSCT for acute lymphoblastic leukemia (S. Giebel) Results of uni- and multivariate analyses revealed significant and independent effect of health care expenditure (HCE) and human development index (HDI) on early and overall NRM. The manuscript is in preparation
- Can JACIE accreditation overcome the impact of socio-economic status and center experience on results of alloHSCT (S. Giebel, T. Czerw). The effect of JACIE accreditation on results of alloHSCT has already been reported. Longer follow-up is needed to re-evaluate it.
- Center effect impact on outcomes after HLA matched HSCT for AML in France (J. Rossignol; S. Katsahian)

### Proposals

- Non-relapse mortality after alloHSCT for ALL according to donor type and age groups (S. Giebel). Indications for alloHSCT in adult ALL are currently discussed by the European collaborative groups. The most recent data on NRM are awaited and may determine the role of alloHSCT in ALL.

### **Auto-HSCT (Leader: Pr. NC Gorin):**

#### Ongoing study

- Long-Term Follow-up of Autologous Hematopoietic Stem Cell Transplantation (AHSCT) for Acute Myeloid Leukemia (AML): A Survey of 3567 Patients From the ALWP (T. Czerw). Results of a survey indicate that even after more than 2 years after autoHSCT there is still considerable risk of relapse (16% at 10y). The manuscript is in preparation.
- Autologous versus haplo transplant in AML (NC. Gorin). Retrospective matched-pair analysis has been performed suggesting that results of haploHSCT and autoHSCT may be comparable. In particular, no advantage of haploHSCT over autoHSCT with regard to LFS could be demonstrated in AML CR1 with IR karyotype. A prospective, randomized study restricted to IR AML in CR1 MRD(-) is postulated. Manuscript submitted
- Various transplantation options for ALL >55 years old (S. Giebel). A retrospective analysis including over 1000 patients indicates that all MAC-allo, RIC-allo and autoHSCT are performed in this setting. AutoHSCT is associated with the highest probability of LFS. Collection of additional data on Ph-status is needed followed by a multivariate analysis. (oral presentation during the EBMT meeting)

### **Reduced Intensity Conditioning (RIC) (Leader: Pr. A. Nagler):**

#### Ongoing studies

- Comparison of FB2 versus FB4 in alloHSCT for AML in CR1 (M. Kharfan-Dabaja, M. Mohty). No apparent differences have been demonstrated between results of FB4 vs. FB2 for AML in CR1. (accepted for publication in "Bone Marrow Transplant")
- Significance of Busulfan Dose Intensity On Outcomes of Hematopoietic Cell Allografting for AML in Second Complete Remission or Beyond (A. Bazaarbaqi, M. Kharfan-Dabaja, M. Mohty). According to preliminary analysis FB4 is a reasonable preferred conditioning in patients with AML in  $\geq$ CR2 (better LFS). Collection of missing cytogenetic data is important.
- Effect of conditioning intensity on outcome of AML with monosomal karyotype transplanted in CR1 in patients over 50 year-old (X. Poiré). Database is completed. Statistical analysis is planned.
- Impact of the intensity of prophylactic immunosuppressive therapy in genotypical allo-SCT for AML conditioned with a Flu-Bu2 regimen (MT Rubio). EBMT 2014 Oral presentation
- Data mining study (R. Shouval). Based on "data mining" methodology a model has been created allowing for estimation of mortality after alloHSCT. The on-line tool is available on the EBMT website. However, the model still requires external validation. (oral presentation during the ASH 2013 and EBMT meeting, manuscript in circulation)
- iv Bu-Cy vs Cy-TBI in advanced phase/relapsed AML (A. Nagler). In advanced disease there may be advantage of TBI-based conditioning.
- Survey on the use of Treosulfan as part of the conditioning regimen in ALL and AML (A. Nagler). 795 AML patients treated with treosulfan in various combinations were included in

the analysis. Results will be presented during the ASH meeting. (oral presentation during the ASH 2013 meeting)

- Comorbidities score (J. Verluise & J. Cornelissen). Based on analysis of 812 patients treated with RIC-HSCT in CR1 a new prognostic model based on co-morbidities has been created. It allows better prediction of NRM compared to the EBMT score and CI-HCT. (oral presentation during the ASH 2013 meeting, accepted for publication in "Leukemia").
- Impact of dose intensity in RIC allo-SCT for ALL: a joint EBMT and CIBMTR study (M. De Lima; R. Ashley; M. Mohty). Data have been forwarded to CIBMTR.
- Allogeneic transplantation to treat secondary AML diagnosed after autologous transplant (L. Metheny, M. de Lima). CIBMTR joint study proposal. Data have been forwarded to CIBMTR
- RIC versus MAC in AML CR1 adjusted for comorbidities, cytogenetics and age (J. Passweg). Results of the analysis indicate that among patients with AML in CR1, aged 40-60 years results of RIC-alloHSCT are not inferior to MAC-alloHSCT. (oral presentation during the ASH 2013 and EBMT meeting)

### Proposals

- Haploidentical stem cell transplantation in acute leukemia outcome after ablative vs. non-ablative conditioning regimens (B. Savani). The study is feasible and may be performed based on already collected data.
- Survival Advantage for Patients with AML and MDS given Allo-SCT Using MAC Versus RIC May Become Apparent 5-10 Years After Transplantation: RIC Studies May Need to be Revisited After Long-Term Follow-up (A. Shimoni). The study will be based on the same set of patients as published in Leukemia 2005.
- Comparison of two RIC regimens for allo-HSCT as treatment for acute myeloid leukemia (F. Baron); feasibility is OK.

### **Molecular Markers (Leader: Dr. J. Esteve):**

#### Ongoing studies

- Impact of NPM1 & FLT3-ITD mutational status on the outcome of alloHSCT for normal cytogenetics AML (C. Schmid). According to initial analysis results of NPM1wt/FLT3-ITD(-) are good and comparable to NPM1(+)/FLT3-ITD(-). Final analysis requires collection of additional data including the number of consolidation courses, the use of HD-AraC, EBMT-score, CEBPA mutation status. (oral presentation during the ASH 2013 meeting)
- HSCT for APL in the ATO era (J. Sanz, J. Esteve). An analysis of 89 patients treated with HSCT in CR2 indicates relatively good results, comparable for auto and allo-transplantations.
- Outcome of alloHSCT for Ph(+)-ALL in CR1 in the era of TKIs (E. Brissot). In a large analysis including 473 alloHSCT recipients the use of pre-transplant TKI was associated with reduced risk of relapse and increased LFS. (oral presentation during the EBMT meeting , the manuscript has been submitted for publication)
- Outcome of alloHSCT for T-ALL (X. Cahu). Significant advantage of TBI- vs. chemotherapy-based conditioning has been demonstrated, especially for patients with advanced disease. The manuscript has been submitted for publication.
- Auto vs. ATO (C. Ganzel). CIBMTR joint study. Data have been forwarded to CIBMTR.

### Proposals

- Predictive determinants of outcome following allogeneic hematopoietic cell transplantation for AML with normal karyotype and isolated NPM1 mutation (A. Bazarbachi, M. Kharfan-Dabaja); study feasible based on already available data.

- Survey on treatment with FLT3 inhibitors for relapsed FLT3-ITD AML after alloHSCT (J. Esteve)
- AlloHSCT in AML with 3q26 (EVI1) rearrangement (K. Halaburda). Form for data collection has been prepared. The aim is to assess the efficacy and predictors of response. Data from previous EBMT studies could be used for the analysis in addition to approaching national study groups.
- Comparative analyses of different post-remission strategies (alloHSCT vs. other) for patients with intermediate-risk AML and triple negative genotype: an AMLSG and EBMT joint study (R. Schlenk, J. Esteve). The study assumes cooperation of the ALWP with national study groups. AMLSG and PALG declared their contribution. Other groups should be approached.
- Acute biphenotypic leukemias (R. Munker) CIBMTR joint study. Initial search of the EBMT and CIBMTR database revealed app. 900 patients with biophenotypic leukemia. The study is feasible. As number of patients in the EBMT registry is twice higher compared to CIBMTR it is expected that CIBMTR data will be transferred to EBMT. Technical issues are to be discussed.
- Outcome of allogeneic stem cell transplantation for acute myeloid leukemia in first complete remission carrying (17p) abnormalities (X. Poiré). Study feasible based on already collected data.

### Alternative Donors (Leader: Dr. F. Ciceri):

#### Ongoing studies

- Impact of NIMA in MUD alloHSCT for AML (A. Schmidt, J. Pingel). Data forwarded to CIBMTR). In EBMT 832 donor were contacted, 373 maternal samples received, 12 NIMA match cases (9/10 Match), 17 pot. NIMA match cases in need for further clarification (HLA-typing). Further data collection is ongoing.
- Survey on unmanipulated graft haploidentical transplantation (S. Piemontese). 202 patients were included in the analysis. Best results are achieved for bone marrow transplants without the use of ATG. Results will be presented during ASH meeting. The manuscript is in preparation.
- Equivalent Outcome between Older Siblings and Unrelated Donors After RIC Allo HSCT for Patients Older Than 50 Years with AML in CR1 (R. Peffault de Latour). The manuscript has been submitted for publication.

#### Proposals

- HLA-DP functional matching in unrelated donor SCT: proposal of a prospective study (K. Fleischhauer). The aim is to determine prognostic value of 'permissive' and 'non-permissive' mismatches. Italian and German donor registries have been approached.
- Allogeneic hematopoietic stem cell transplantation with alternative donors in patients with poor risk AML in CR1 (J. Versluis). The aim is to compare results of CBT and haploHSCT. The study is feasible provided that will be based on already available data.
- Comparison of CBT vs HaploSCT in acute leukemia (A. Ruggeri).
- Matched and Mismatched Unrelated Donor versus Unmanipulated Haploidentical graft from family donors for hematopoietic stem cell transplantation in acute leukemia: a comparative analysis on the behalf of EBMT-ALWP (S. Piemontese).

Mohamad Mohty  
Chairman of the ALWP

Sebastian Giebel  
Secretary of the ALWP

