

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

<b>Location:</b>	Paris, France	<b>Date:</b>	27/11/2015
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<b>Author:</b>	Sebastian Giebel, Arnon Nagler
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<b>Participants:</b>	EBMT:	Baron Frédéric; Bazarbachi Ali; Bentsen Pål Tore; Beohou Eric; Boumendil Ariane; Brissot Eolia; Brune Mats; Brunet Mauri Salut; Bug Gesine; Craddock Charles; Czerw Tomasz; Devillier Raynier; Floisand Yngvar; Giannotti Federica; Giebel Sebastian; Gorin Norbert Claude; Guimaraes Jose Eduardo; Gulbas Zafer; Halaburda Kazimierz; Hicheri Yosr; Houhou Mohamed; Ivanovski Martin; Labopin Myriam; Laroulandie Martine; Lorentino Francesca; Mailhol Audrey; Mamaev Nikolky; Maximova Natalia; Mohty Mohamad; Nagler Arnon; Pavlu Jiri; Penisson Eva; Poiré Xavier; Polge Emmanuelle; Ringden Olle; Rubio Marie-Thérèse; Ruggeri Annalisa; Salamero Garcia Olga; Santoro Nicole; Saraceni Francesco; Savani Bipin; Schmid Christoph; Sengeløv Henrik; Sestili Simona; Shouval Roni; Veelken J.H.; Versluis Jurjen;
<b>Apologies</b>		Ciceri Fabio, Piemontese Simona, Afanasyev Boris

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

### Introduction (ALWP Chair: A. Nagler; ALWP secretary: S. Giebel; ALWP statistician: M. Labopin)

Prof. Arnon Nagler pointed out that acute leukemias remain the most frequent indication for alloHCT and the number of transplants is continuously growing. He 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 in 2013, Paris in 2014 and 2015); (ii) designing and support to prospective clinical trials in the field of acute leukemia across member centres (the elderly AML randomized trial is currently recruiting patients: ClinicalTrials.gov Identifier: NCT00766779); (iii) generation of high quality retrospective studies addressing different issues related to acute leukemia management and therapy; (iv) Increase within the registry the quality of data pertinent to SCT for acute leukemia; (v) generation of guidelines pertinent to management of acute leukemia.

In 2015, the activity of ALWP was reflected by over 20 scientific papers published in Journal of Clinical Oncology, Lancet Haematology, Blood, Leukemia, Haematologica, The Oncologist and other high quality journals. Results of the studies were presented at major congresses such as the EBMT meeting 2015 (including 9 oral presentations). Seven abstracts have been accepted for oral presentation during the ASH 2015 meeting.

So far structure of ALWP includes 7 subcommittees: Autologous SCT (NC. Gorin), Immunotherapy (C. Schmid), Alternative donors (F. Ciceri), RIC allo-SCT (B. Savani), Molecular markers (J. Esteve), Acute lymphoblastic leukemia (S. Giebel), and Cord blood (F. Baron).

The next business meeting and educational symposium is planned during the EBMT meeting in Valencia on 04.04.2016, between 7 am – 9 am.

New study proposals are kindly invited. They should be addressed either to the ALWP chairman or subcommittee appropriate leader (see: email addresses at the end of the minutes).

### Activity of the subcommittees:

#### Acute Lymphoblastic Leukemia (Leader: Pr. S. Giebel):

##### Papers accepted for publication

- Outcome of alloHSCT for T-ALL (X. Cahu). Results of sibling and unrelated donor HSCT are comparable; TBI-based conditioning has advantage over chemotherapy in T-ALL. Accepted by *Bone Marrow Transplant*, in press.
- Impact of socio-economic factors on non-relapse mortality after alloHSCT for acute lymphoblastic leukemia (S. Giebel). Health care expenditure and human development index of a country influence NRM after alloHSCT for ALL. Accepted by *The Oncologist*.

##### Papers submitted/in preparation

- Improving results of alloHSCT for adults with ALL (S. Giebel). The outcome after both MSD-HSCT and URD-HSCT improved significantly in almost all age groups. TBI is still associated with reduced risk of relapse and better LFS. Submitted for publication to *JCO*.
- AlloHSCT for patients older than 60 years (G. Roth). RIC-alloHSCT is a feasible option for ALL patients aged >60 years. Advanced disease status and the use of URD affect LFS. Paper in preparation.
- Recommendations on the use of TKIs after alloHSCT in patients with Ph-positive ALL. Paper in preparation.

##### Ongoing Studies

- RIC-alloHSCT vs autoHSCT in elderly patients with ALL (S. Giebel). According to preliminary analysis both RIC-alloHSCT and autoHSCT are valuable options in this high risk patient population. In this analysis AutoHSCT is associated with increased LFS. Data collection is ongoing.
- Allogeneic hematopoietic stem cell transplantation for primary refractory acute lymphoblastic leukaemia. (J. Pavlu). In the era of new drugs the role of alloHSCT in PIF should be re-evaluated. Data collection is ongoing.
- Survey on the use of thiotepa as part of the conditioning regimen in ALL (S. Eder). Promising results of thiotepa-based regimens. Poster at *ASH 2015*.
- Thiotepa vs TBI as part of the conditioning regimen in ALL (S. Eder). Abstract prepared for the *EBMT 2016*.

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

##### Papers submitted/in preparation

- Impact of CD3+ cell dose on outcome after RIC-alloHSCT for AML (T. Czerw). Both CD3 and CD34 dose influence the risk of GVHD after RIC-alloHSCT. Rejected by *Blood*, will be resubmitted.

- Use of azacitidine after alloHCT for AML (C. Craddock). The paper demonstrates the ability of AZA to salvage a proportion of patients with AML or MDS who relapse after an allogeneic SCT. In selected patients CR rates achieved with salvage AZA are comparable to those previously reported with either intensive chemotherapy or DLI. The manuscript has been rejected by Blood. It will be resubmitted to *Haematologica*.
- Determinants of the kinetics of disease relapse after an allograft for AML (C. Craddock). A complex interaction of disease specific and transplant factors determine the kinetics of relapse post-transplant. The paper is in circulation.
- Sequential Chemotherapy Followed by RIC allo-SCT in Adult Patients with Relapsed or Refractory AML (O. Ringden). Over 300 patients have been identified. The paper is in circulation.

### Ongoing Studies

- Pre-emptive or prophylactic use of DLI (C. Schmid). Pre-emptive DLI used for mixed chimerism or MRD-positivity is associated with 69% success rate. Prognostic factors for acute GDVH have been identified. Next steps: matched-pair analysis of „pure prophylactic“ DLI with patients not receiving it, intensification on the prospective part (NIS), finishing the online survey on “general center strategy”. Oral presentation at *ASH 2015*.
- Second allograft versus DLI in relapsed AML (M. Kharfan-Dabaja). Data collection is ongoing.
- The risk of relapse after HaploHCT (C. Schmid; S Piemontese). Preliminary analysis was performed indicating prolonged survival for late vs. early relapse. Data collection is ongoing.
- Sequential intensified conditioning regimen + alloHCT in adults with high-risk AML in CR (F. Malard). No difference between FLAMSA-TBI and FLAMSA-Bu based regimen. No difference between CR1 vs. CR2 and between de novo AML vs. sAML. Poster at *ASH 2015*.
- Second alloHCT vs. DLI for relapsed AML (C. Schmid). Data collection is ongoing.

### Proposals

- Clinical trial: Panobinostat for prevention of relapse post alloHCT in high risk AML (G. Bug). There is interest from study groups (e.g. PALG). There was suggestion to exclude haploHCT and to randomize patients on day 60 after alloHCT. Various conditioning regimens and various immunosuppression protocols may be accepted. The protocol will be further discussed.
- Extramedullary relapse (M.D.S. Aljurf). The goal is to analyse the incidence, risk factors, and clinical outcomes of extramedullary relapse post allogeneic HCT for AML and ALL. The study is rather not feasible due to difficulties with data collection.

### Subcommittee: Autologous HSCT (Leader: Pr. N.C. Gorin)

#### Papers submitted/in preparation

- Long-Term Follow-up of Autologous Hematopoietic Stem Cell Transplantation (AHCT) for Acute Myeloid Leukemia (AML): A Survey of 3567 Patients from the ALWP (T. Czerw). Results of autoHSCT for AML patients are enhancing, however, late relapses remain a concern. Submitted to *Eur J Haematol*.
- AutoHSCT for adult AML in CR1: better outcome following busulfan and melphalan compared to busulfan and cyclophosphamide (N.C. Gorin). Oral presentation at *ASH 2015*; paper is about to be circulated.
- Autologous versus unrelated HSCT in Acute Leukemia (F. Saraceni). Both procedures have potential in AML CR1. The aim is to find “the best spot for AutoHSCT and URD-HSCT with a “tailored therapy” approach. Preliminary analysis show no significant differences between

auto URD 10/10 matched and URD 9/10 matched transplantations, however the effect may vary according to the karyotype risk groups. Poster at *ASH 2015*. Paper is in preparation.

### Ongoing Studies

- Updating the follow-up of AutoHSCT for AML (N.C. Gorin). Data of AML patients in CR1 or CR2 treated with autoHSCT between 1990-2014 are going to be updated. Data on 3564 out of expected 4440 have been collected. The data collection is ongoing.

### Proposals

- Conditioning in Autologous Stem Cell (N.C. Gorin, T. Czerw). The impact of various conditioning regimens on outcome will be analysed in a setting of autoHSCT for AML in CR1 and CR2. The study is feasible.
- The impact of MRD status on the outcome of autoHSCT for AML in CR1 and CR2 (T. Czerw). Due to heterogeneity of methods used for MRD evaluation and potential difficulties in data collection the study is rather not feasible.
- AlloHSCT following relapse post autoHSCT (M. Christopeid). The study is potentially feasible. Detailed synopsis is needed.

### Subcommittee: Conditioning (RIC) (Leader: Dr B. Savani)

#### Papers submitted/in preparation

- Influence of stem cell source (bone marrow versus peripheral blood) on outcome after reduced-intensity conditioning regimens for acute leukemia (B. Savani). Transplants with PB from matched or MM related or unrelated donor after RIC give the best outcomes. However, increased risk of cGVHD after PB grafts is alarming and long-term follow-up is needed to see if cGVHD related deaths might increase risk of late NRM. Accepted for publication in *Haematologica*.
- MMUD-HSCT in acute leukemia after myeloablative vs. non-myeloablative conditioning (M.T. Rubio). No significant outcome difference between RIC and MAC regimens after MM URD allo-SCT in pts younger than 50 years. Submitted for publication.
- Influence of HLA-matching after reduced conditioning regimen and unrelated donor allo-SCT for acute myeloid leukemia in patients older than 50 years. (B. Savani, M.T. Rubio). No significant outcome difference between 9/10 and 8/10 MM-URD allo-SCT after RIC regimen in patient aged  $\geq 50$  year. Paper in preparation.
- Relapse of Acute Myeloid Leukemia after Hematopoietic Stem Cell Transplantation: Methods of Monitoring and Preventive Strategies (P. Tsirigotis). Submitted for publication.
- Survey on the use of Treosulfan as part of the conditioning regimen in ALL and AML (A. Nagler, B. Savani). Paper is being written.
- 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). Paper is being written.

### Ongoing Studies

- Impact of conditioning regimen intensity on transplant outcome for secondary acute myeloid leukemia (A Nagler, Labopin M, B Savani). Oral presentation at *ASH 2015*.

### Proposals

- FB4 in siblingHSCT, ATG vs. no ATG (M.T. Rubio). According to the preliminary analysis the use of ATG is associated with increased OS, LFS and GRFS, while reduced risk of cGVHD. Collection of additional data on cytogenetics and ATG doses is needed.
- Impact of HLA high resolution typing on outcome of RIC-URD-HSCT for AML (C. Craddock). The issue is important, however, data collection may be difficult. Detailed synopsis is needed.
- Comparison of outcomes between reduced intensity and myeloablative conditioning in AML and MDS patients with complex cytogenetics (S. Ciurea, B. Savani, A. Nagler). The proposal for collaboration with CIBMTR, will be discussed during the ASBMT Tandem Meeting in February 2016.
- BuCy vs. BuFlu as conditioning before alloHSCT for patients with AML (M. Aljurf). Results of two randomized trials have been published. There is no rationale to perform a retrospective analysis.

### Subcommittee: Molecular Markers (Leader: Dr Jordi Esteve)

#### Papers submitted/in preparation

- AlloHSCT in CR1 for patients with AML associated to a monosomal karyotype (A.V.M. Brands-Nijenhuis, F. Malard). Accepted for publication by *Haematologica*.
- Comparative analyses of different post-remission strategies (alloHSCT vs. other) for patients with intermediate-risk AML and triple negative genotype: a CETLAM, AMLSG and EBMT joint study (R. Schlenk, J. Esteve). AlloHSCT in first CR is associated with a marked relapse reduction and survival benefit compared to CHT or autoHSCT in the two cooperative group cohorts with prospective treatment data as well as in the whole cohort including the EBMT registry data. The paper is in preparation.
- HSCT for APL in the ATO era (C. Ganzel, J. Esteve). An analysis of 120 patients indicates better OS and LFS for autoHSCT compared to ATO group. Joint study with CIBMTR. Oral presentation at *ASH 2015*. The paper is in preparation.
- AlloHSCT in AML with 3q26 (EVI1) rearrangement (K. Halaburda). An analysis including 106 patients indicate poor outcome with relapse being the major cause of treatment failure. Oral presentation at *ASBMT Tandem meeting 2016*.
- Comparison of MSD- vs. URD-alloHSCT for primary refractory AML (E. Brissot). 1/3 of patients may be rescued. No difference between to types of donors. Oral presentation at *ASH 2015*. The paper is in circulation.

#### Ongoing Studies

- Allogeneic stem cell transplantation for patients over 60 years or older with acute myeloid leukemia with normal karyotype and internal tandem duplication of FLT3 (X. Poiré). Poor outcome due to high incidence of relapse. Poster at *ASH 2015*.
- Acute biphenotypic leukemias (R. Munker). Data on immunophenotyping are lacking. Detailed study synopsis is requested.
- AlloHSCT for Ph-positive AML (V. Lazarevic). 232 patients have been identified. Additional data collection regarding the use of TKIs is necessary.

#### Proposals

- Outcome of stem cell transplantation in adult patients with Core Binding Factor AML transplanted in second complete remission (K. Halaburda). The study is feasible.

- Relapse after alloHCT for FLT3-ITD AML: role of sorafenib (A. Bazarbachi, C. Schmid). 969 patients with relapse after alloHSCT have been identified. The study would require additional data collection.

### Subcommittee: Cord Blood (Leader: Dr F. Baron)

#### Papers submitted/in preparation

- Impact of conditioning intensity on cord blood transplantation outcomes in acute leukemia patients, on behalf of Eurocord-EBMT (F. Baron). There is suggestion to prepare separate analysis for ALL. Oral presentation at *ASH 2015*. The paper is in circulation.
- Analysis of risk factors for unrelated double unit cord blood transplantation in adult patients with acute leukemia, on behalf of Eurocord-EBMT (F. Giannotti). 347 patients have been included. The type of the “winning” CB unit influences outcome. 4/6 HLA-matched “winning” CB is associated with decreased OS and LFS. Poster presentation at *ASH 2015*. Paper is in preparation.

#### Ongoing Studies

- Umbilical Cord Blood Transplantation Outcomes in FLT3 Mutation Positive Patients with Acute Myelogenous Leukemia, Proposal from University of Minnesota- Eurocord- EBMT. (C. Ustun). The goal is to retrospectively evaluate UCBT outcomes in pts with FLT3+AML transplanted at the University of Minnesota or reported to CIBMTR, or transplanted at an EBMT center and reported to Eurocord. Data has just been received and will be analyzed soon.
- A data mining approach to predict 1-year mortality in cord blood transplantation for AML (R Shouval). It is assumed that given potential advantages of machine learning techniques, applying them on UCBT patient data will lead to the development of robust prediction models for 1 year TRM. Poster at *ASH 2015* (awarded).
- Single vs. double UCBT in patients given RIC for AL. A study by the EUROCORD and the ALWP of the EBMT (F. Baron). The study is feasible. Statistical analysis based on available data may be performed soon. An abstract will be prepared for the *EHA 2015* meeting.

#### Proposals

- Impact of donor type (MSD, MUD, MMUD, Haplo, UCB) on transplantation outcomes in patients with sAML (F. Baron). The feasibility of the study needs further evaluation.
- Incidence and risk factors for SOS/VOD after UCBT for AML: an analysis of the ALWP of the EBMT and UEROCORD. (F. Baron). The feasibility of the study needs further evaluation.
- Revisiting graft-versus-leukemia effects after UCBT for AML: an analysis from the ALWP of the EBMT and from Eurocord (F. Baron). The idea is to assess the evolution of the impact of aGVHD (grade 1, grade 2, grade 3-4) and of chronic GVHD (limited versus extensive) on other UCBT outcomes in AML patients by comparing rate of relapse per patient-year for each condition (no GVHD, grade II-IV acute GVHD and no chronic GVHD, grade II-IV acute GVHD and chronic GVHD, or chronic GVHD only) within sequential 90-day intervals after allo-SCT.
- Comparison of UCBT and unmanipulated haplo-HSCT after TBF conditioning regimen, for adults with AML, on behalf of Eurocord-EBMT (F. Giannotti). Preliminary analysis indicates reduced risk of NRM and improved survival after haplo-HSCT compared to UCBT. Additional data collection for centers is required.

### Subcommittee: Alternative Donors (Leader: DR F. Ciceri)

### Papers submitted/in preparation

- Refined GRFS for registry based studies (A. Ruggeri). A new study end-point has been proposed combining, in which patients experiencing grade III-IV aGVHD, cGVHD, relapse or death in remission are considered completed observations. GRFS may be used for many studies, including comparisons of allo- vs. autoHSCT. Pre-published on-line in *Bone Marrow Transplant*.
- Comparative study of HLA id sibling versus MUD for adults with relapsed acute leukemia (A. Ruggeri). URD-HSCT is associated with better LFS due to lower RI compared to MSD-HSCT for high-risk patients with AML transplanted in first relapse. The paper is in preparation.
- HLA mismatches in T-cell replete haplo-HSCT (F. Lorentino). Number of HLA mismatches on unshared haplotype is not predictive for outcome. Oral presentation at *ASH 2015*. Paper is being circulated.
- Impact of the different GVHD prophylaxis (ptCy vs. ATG) on outcomes of unmanipulated HaploHSCT (A. Ruggeri). The analysis included 308 patients. PtCy is associated with improved LFS and GRFS. The paper is in preparation.

### Ongoing Studies

- Allogeneic hematopoietic stem cell transplantation with alternative donors in patients with poor risk AML in CR1 (J. Verluis, J. Cornelissen). For patients with HR AML in CR1 results of MSD-HSCT, 10/10 URD-HSCT and haplo\_HSCT are comparable. The outcome after 9/10 URD-HSCT and UCBT is worse. Additional statistical analyses are needed prior to publication.
- Impact of NIMA in MUD alloHSCT for AML (A. Schmidt; J. Pingel). The study in collaboration with DKMS and CIBMTR. Poster at *ASH 2015*.
- Match pair analysis Haplo versus Mud in poor-risk cytogenetic AML in CR (F. Lorentino). Data collection is ongoing. An abstract will be prepared for the *EBMT 2016* meeting.

### Proposals

- GRFS after TCD and non-TCD haplo-HSCT (S. Sestilli). 1040 patients have been identified. An abstract will be prepared for the *EBMT 2016* meeting.
- Risk factor analysis of non-T-cell depleted haplo-HSCT for adults with ALL (N. Santoro). The study is feasible. 271 patients have been identified. Data on cytogenetics need to be collected in 119 cases.
- Haplo-HSCT vs. URD-HSCT in PIF and CR1 AML (E. Brissot). An abstract will be prepared for the *EBMT 2016* meeting.

### Various proposal/studies

#### Papers submitted/in preparation

- *In Silico* for analysis of transplant outcome in AML (Souval R, Nagler A). The manuscript has been rejected by *Leukemia*. It will be resubmitted.
- Survey on the use of Thiotepa as part of the conditioning regimen in AML (S. Eder). The paper has been resubmitted to *Haematologica*.
- Impact of ATG dose and timing on allo-SCT outcome (R. Devillier). Higher doses of ATG are associated with increased risk of relapse in AML CR1 after MSD-HSCT. The paper is in circulation.

### Ongoing Studies

- Impact of previous gemtuzumab administration on the incidence of VOD after allo-SCT in AML. Data collection is ongoing.

### Proposals

- GRFS in AML patients receiving allogeneic HSCT from HLA-identical and unrelated donors (G. Battipaglia).
- Haplo-HSCT after a previous CBT and CBT after a previous haploHSCT (A. Nagler, A. Ruggeri).

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