MINUTES OF MEETING

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

Location:	Marseille, France	**Date:**	22/11/2013

Author:	Sebastian Giebel

Participants:	EBMT:	Aljurf Mahmoud; Arby Tania; Baron Frederic; Bernardini Massimo; Blaise Didier; Bonini Chiara; Bramanti Stefania; Brunet Salut; Bug Gestine; Castagna Luca; Cornelissen Jan; Czerw Tomass; El Cheikh Jean; Essink Monica; Esteve Jordi; Finel Herve; Floisand Yngvar; Fuchs Ephraim; Giannoli Gilles; Giebel Sebastian; Girshova Larisa; Gorin Norbert-claude; Guimaraes Jose Eduardo; Halaburda Kazimierz; Hemmati Philipp; Hicheri Yosr; Jongen-Lavrencic Mojca; L Houssni Amina; Labopin Myriam; Laroulandie Martine; Legrand Faizeh; Lamaia Elza; Mc Donald Andrew; Mohty Mohamad; Mohty Bilal; Moukhtari Leila; Munker Reinhold; Nagler Arnon; Pavlu Jiri; Perez Requejo Isabel; Piemontese Simona; Poiré Xavier; Polge Emmanuelle; Ringden Olle; Rubio Marie-therese; Ruggeri Annalisa; Schmid Christoph; Shouval Roni; Stute Norbert; Svahn Britt-marie; Ta Thanh Minh Christine; Thomson Jackie; Versluis Jurjen; Vrhovac Radovan; Yeshurun Moshe; Zafer Gülbas;
	Other:	
Apologies		Ciceri Fabio

Distribution:	EBMT members

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, and Milan in 2012); (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.

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).

Everyone is welcome to participate in the activity of ALWP and to submit the study proposals as synopsis sent to either chairman (M. Mohty), secretary (S. Giebel) or subcommittee leader. The

proposals will further be evaluated in terms of the scientific merit, financial aspects, and the feasibility from the point of view of statistical analysis and data management.

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New ALWP chairman election; candidates endorsment

Elections for a new ALWP chairman are planned before the EBMT congress in Milan 2014. Current chairman, prof. Mohty presented two candidates: prof. Sebastian Giebel (Gliwice, Poland) and prof. Arnon Nagler (Tel-Hashomer, Israel). Both candidates have been 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. Results of the survey will be presented during ASH meeting (poster) (manuscript in preparation).
- 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. Results will be presented during ASH meeting (poster).

Prospective ALWP trials

<u>Ongoing prospective study</u>

- Randomized comparison of RIC vs. chemotherapy as post-remission therapy in elderly patients with AML (D. Niederwieser, M. Mohty). This is the first prospective, randomized study to evaluate the role of RIC-alloHSCT in elderly AML. More than 100 patients have been recruited so far.

<u>Proposals</u>

- A multi-center, phase III, randomized trial of umbilical cord blood (UCB) versus HLA-haploidentical related stem cell transplantation for patients with hematologic malignancies (M. Mohty). The study would include adults <65 years. The conditioning in both arms would be TBF + ATG and GVHD prophylaxis – CsA + MMF. Patients in the haplo arm would receive

additionally post-transplant cyclophosphamide. Primary end-point of the study would be the rate of platelet engraftment on day 60, which requires recruitment of app. 35-40 patients per arm. The study was assessed as feasible, however, the choice of the primary end-point was a subject of discussion.

- A multi-center, phase III, randomized trial of matched unrelated versus HLA-haploidentical related stem cell transplantation for patients with hematologic malignancies (D. Blaise). The study would include patients over 60 years old, treated with RIC. Patients with high probability of finding MUD would be referred for unrelated donor search, while those with low chance would receive haploHSCT with post-transplant use of cyclophosphamide. OS without GVHD at 1 year would be the primary study end-point. The proposal raised big interest. Details of the protocol will be further discussed.

Activity of the subcommittees:

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

Completed studies

- AutoHSCT for ALL (S. Giebel). In Ph-positive ALL dramatic improvement over time has been found suggesting that introduction of TKIs in recent years decresed relapse rate. AutoHSCT in the TKI era appears a potentially curative option (published in Eur J Cancer 2013).
- Granulocyte colony-stimulating factor after autologous hematopietic stem cell transplantation for acute myelocytic leukemia – association with outcome (T. Czerw). Results indicate that post-transplant use of G-CSF has no impact on long-term results. G-CSF may be used in this setting without increasing the risk of relapse (manuscript under revision).
- 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) (manuscript is in preparation).

Ongoing study

- 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.

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

Completed studies

- The impact of center experience on results of reduced intensity:allogeneic hematopoietic SCT for AML. An analysis from the ALWP of the EBMT (S. Giebel). Results of RIC-HSCT are significantly worse in centers with very low activity. Center experience is an independent factor affecting outcome, which should be taken into account when interpreting results of studies on RIC-HSCT (published in Bone Marrow Transplant 2013).
- Results of allogeneic HSCT for patients with acute myeloid leukemia (AML): comparison of EMBMT and EBMT participating centers (A. Bazarbachi). Results of siblingHSCT for AML in CR1 are comparable for EBMT and EMBMT. (published in Bone Marrow Transplant 2013).
- Impact of socio-economic factors on non-relapse mortality after alloHSCT for acute lymohoblastic 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. Results will be presented during ASH meeting (poster) (manuscript in preparation).

Proposals

- Can JACIE accreditation overcome the impact of socio-economic status and center experience on results of alloHSCT? (S. Giebel). Feasibility of this study has been discussed. It is expected that JACIE accredited centers are usually more experienced and located in countries with higher HCE and HDI. Hence the analysis may be difficult.
- Center effect impact on outcomes after HLA matched HSCT for AML in France (S. Katsahian).

Immunotherapy (Leader: Dr. C. Schmid):

Completed studies

- Second allograft versus DLI in relapsed AML (M. Kharfan-Dabaja). Results will be presented during ASH meeting (poster).
- Long term results after second transplant for relapsed AML (G. Andreoli). Analysis has been performed. The manuscript is in preparation and should be ready before the end of the year.

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 unrestriced grant from Celgene. So far 258 patients have been reported.
- 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.

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. It was suggested and accepted to restrict this analysis to patients with ALL.
- 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 immonusuppression are needed. They may be collected by asking centers for their strategies. Hence, individal patient-oriented queries are not necessary and the study appears feasible.
- Factors affecting the kinetics of disease relapse after an allograft for AML (C. Craddock, M. Yesherun). Patients with early and late relapses will be compared for characteristics of the disease, conditioning and immune fators. Results of the study may guide post-transplant immune interventions to prevent relapse.
- Impact of CD3+ cell dose on outcome after RIC-alloHSCT for AML (T. Czerw). The impact of graft composition on outcome has not been extensively studied in the setting of RIC-HSCT so far. The goal is to determine the potential threshold of CD3+ cell dose associated with the risk of GVHD. Centers known to perform large number of RIC transplants will be approached.

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

Completed studies

- Allogeneic hematopoietic stem-cell transplantation for acute myeloid leukemia in remission: comparison of intravenous busulfan plus cyclophosphamide (Cy) versus total-body irradiation plus Cy as conditioning regimen -a report from the acute leukemia working party of the European group for blood and marrow transplantation (A. Nagler). For patients with AML in CR iv Bu-Cy appears not inferior to Cy-TBI (published in J Clin Oncol 2013).
- Correlation of number of consolidation courses and outcome after RIC allo-SCT for AML (M. Yeshurun) (published in Cancer).
- Comparison of FB2 versus FB4 in alloHSCT for AML in CR1 (M. Kharfan-Dabaja, M. Mohty). No apparent difference have been demonstrated between results of FB4 vs. FB2 for AML in CR1 (manuscript under revision).

- Prediction of allo-HSCT related mortality in acute leukemia: Generation of a Machine Learning-Based Model Using the Data Set of ALWP of the EBMT (R. Shoval). 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. Results will be presented during the ASH meeting (oral presentation).
- Comorbidities score (J. Verluis & J. Cornelissen). Based on analysis of 812 patinets 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. However, the model requires external validation. Results will be presented during the ASH meeting (oral presentation) (manuscript in preparation).
- Survey on the use of Treosulfan as part of the conditioning regimen in AML (A. Nagler, F. Ciceri, M. Mohty). 795 AML patients treated with treosulfan in various combinations were included in the analysis. Results will be presented during the ASH meeting (oral presentation).
- 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. Results will be presented during the ASH meeting (oral presentation).

Ongoing studies

- Significance of busulfan dose intensity on outcomes of hematopoietic cell allografting for AML in second complete remission or beyond (A. Bazarbachi, M. Kharfan-Dabaja, M. Mohty). According to preliminary analysis FB4 is a reasonable preferred conditioning in patients with AML in ≥CR2 (better LFS) Collection of missing cytogenetic data is important. The priority of the study is moderate.
- 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.
- iv Bu-Cy vs Cy-TBi in advanced phase/relapsed AML (A. Nagler). In advanced disease there may be advantage of TBI-based conditioning.
- Impact of the intensity of prophylactic immunosupressive therapy in genoidentical allo-SCT for AML conditioned with a Flu-Bu2 regimen (M.T. Rubio). According to preliminary analysis regimens including all ATG, CsA and MTX or MMF are associated with increased risk of relapse. However, centers must be approached and asked for reasons of the choice of particular regimens.
- Impact of dose intensity in RIC allo-SCT for ALL: a joint EBMT and CIBMTR study (M. De Lima; R. Ashley; M. Mohty).

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.
- Impact of the level of donor chimerism on outcomes after RIC-alloHCT for acute leukemia at EBMT participating centers (MA. Kharfan-Dabaja). As there are no data on chimerism in the registry the study conduct appears difficult.
- Allogeneic transplantation to treat secondary AML diagnosed after autologous transplant (L. Metheny, M. de Lima). CIBMTR joint study proposal. Collection of karyotype data is necessary to run this study.
- 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). The proposal was assessed as interesting and important.

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

Completed studies

- Impact of FLT3-ITD/NPM1 mutation status in adult patients with acute myelocytic leukemia autografted in first remission (NC. Gorin) (published in Haematologica 2013).
- 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 (manuscript under review).
- Outcome of alloHSCT for T-ALL (X. Cahu). Significat advantage of TBI- vs. chemotherapy-based conditioning has been demonstrated, especially for patients with advanced disease.
- AlloHSCT for AML (MLL) with 11q23 rearrangement (A. Pigneux) (manuscript in preparation).

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. Results will be presented during the ASH meeting (oral presentation).
- Outcome of HSCT for APL in the ATO era (J. Sanz, J. Esteve). An analysis of 89 patients treated with HSCT in CR2 indicate relatively good results, comparable for auto and allo-transplantations.

Proposals

- Survey on treatment with FLT3 inhibitors for relapsed FLT3-ITD AML after alloHSCT (J. Esteve). 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.
- AlloHSCT in AML with 3q26 (EVI1) rearrangement (K. Halaburda). AML with 3q26 is recognized a separate entity according to WHO 2008 classification. Data on 112 patients with this karyotype treated with alloHSCT between 1993-2008 had already been collected. Patients treated in more recent period should be added to perform final analysis.
- 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.
- AutoHSCT vs. ATO for patients with APL in CR2 (C. Ganzel). Data collection is ongoing.
- 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 transfered to EBMT. Technical issues are to be discussed.

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

Completed studies

- Comparison of outcomes after single or double cord blood transplantation in adults with acute leukemia using different types of myeloablative conditioning regimen, a retrospective study on behalf of Eurocord and the Acute Leukemia Working Party of EBMT. (A. Ruggeri) (published in Leukemia 2013)
- 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) (manuscript in preparation).
- Survey on unmanipulated graft haploidentical transplantation (S. Piemontese). 202 patients were included in the analysis. For patients with acute leukemia in CR1 the LFS rate is 46% at 3 years. Best results are achieved for bone marrow transplants without the use of ATG. Results will be presented during ASH meeting (poster).

Ongoing studies

- Impact of NIMA in MUD alloHSCT for AML (A. Schmidt, J. Pingel). In CIBMTR 369 donors were contacted, 173 maternal samples received, 9 NIMA matches identified (9/10 cases). 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). Additional 103 cases from pilot study are needed for outcome data retrieval. Currently data collection of 431 newly identified cases is ongoing.

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 transplantation using alternative donors (CB and haplo) for refractory acute leukemia (M. Mohty).
- 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.

Other proposals/studies:

Completed studies

- Survey on the use of Thiotepa as part of the conditioning regimen in ALL and AML (S. Eder). Results will be presented during ASH meeting (poster).
- For male patients with ALL and AML, who is the best donor? (O. Ringden) (manuscript in preparation).

Ongoing study

- Impact of ATG dose and timing on allo-SCT outcome (D. Blaise). Data colection is ongoing.

Proposals

- The impact of irradiation dose rate on the efficacy and safety of TBI-based myeloablative allogeneic HSCT for acute leukemia (S. Giebel). Results of the TBI survey revealed that irradiation dose rate varies among centers in a range of 2.25 cGy/min – 37.5 cGy/min, which may strongly affect the outcome. A retrospective analysis is planned to explore the effect of dose rate on the efficacy and toxicity of alloHSCT among centers using total dose 12 Gy in 6 fractions.
- Impact of previous gemtuzumab administration in AML patients after allo-SCT (P. Chevallier).

- 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. The study is feasible and scientifically interesting.
- Allogeneic hematopoietic stem cell transplantation for primary refractory acute lymphoblastic leukaemia (J. Pavlu). The issue has not been addressed so far. Results may be particularly interesting in the context of new drugs that may serve as a bridge to transplantation. The study is feasiblle.

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