Minutes of Acute Leukemia Working Party (ALWP) Business Meeting

EBMT Meeting, Milan, Friday 9th, Nov. 2012
10:00AM-05:00 PM

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

Prof. Mohamad Mohty presented data indicating that acute leukemias are the most frequent indication for HSCT in Europe. Major objectives/missions of the ALWP are: a) organization of educational activities pertinent to acute leukemia, b) design and activation of prospective trials in the field of acute leukemias across member centers, c) generation of high quality retrospective studies addressing different issues related to acute leukemia therapy, d) increase within the registry the quality of data pertinent to SCT for acute leukemia, e) generation of guidelines pertinent to management of acute leukemia. Among major achievements are: a) organization of 5 international educational symposia: Nantes 2008, Barcelona 2009, Milan 2010, Warsaw 2011 and currently in Milan; the 2012 ALWP symposium "Novel agents in stem cell transplantation" provided comprehensive review of agents used for pre- and post-transplant care as well as novel cellular therapies, b) conducting prospective study on the role of RIC transplant for elderly AML, for which 95 patients have been registered so far, c) 13 high quality peer-reviewed publications in 2012, d) 51 oral communications during the EBMT and ASH meetings between 2009-2011; 4 abstracts have been accepted for oral presentations during the ASH meeting 2012.
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.

Auto-HSCT Subcommittee (Leader: Prof. N.C. Gorin)

On-going studies:

- Granulocyte colony-stimulating factor after autologous hematopietic stem cell transplantation for acute myelocytic leukemia – association with outcome (T. Czerw). The analysis including 2093 patients revealed no impact of G-CSF administration on results of autoHSCT for AML in CR1, which indicates that G-CSF may be administered safely in this setting. The data are sufficient to prepare publication.
- Autologous HSCT for ALL. The role of post-transplant maintenance (S. Giebel). Registry-based analysis showed marked improvement in results of autoHSCT for Ph(+) ALL performed between 2007-2010 compared to preceding periods, which could be a consequence of the introduction of pre- and post-transplant TKIs (results will be presented during the ASH meeting). Further investigation is needed to confirm this hypothesis and to evaluate results in the context of MRD status. The questionnaires have been distributed among centers. Study on Ph(-) ALL could be the next step.
- 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). A significant proportion (16%) of patients surviving disease-free 2 years after autoHSCT is still at risk of relapse, which is increased with higher age, the use of PBSC and FAB M067. This

important message justifies preparing publication. Additional data should, however, be collected to verify if late relapses were not second leukemias. EORTC could be approached to facilitate data collection.

Other proposal:

- Non interventional observational study of Azacytidine maintenance therapy following autologous SCT for AML (NC. Gorin). Design of the study was presented raising discussion on the inclusion criteria (should the population be restricted to MRD-neg cases of NPM1-pos FLT3-ITDwt AML or also MRD-pos) and nature of the investigation (interventional rather with regulatory implications).

Developing centers Subcommittee (Leader: S. Giebel):

Ongoing studies:

- Impact of economical factors on results of alloHSCT (S. Giebel). Study on alloHSCT in ALL CR1 identified health care expendirure, team density, team experience and HDI as factors influencing outcome. Unfortunately for vast majority of patients Ph-status is unavailable from the database. Additional short query could be addressed to centers. Continuation of the study depends on manpower of AWLP.
- Results of allogeneic HSCT for patients with acute myeloid leukemia (AML): comparison of EMBMT and EBMT participating centers (A. Bazarbachi). In a matched-pair analysis results of sibling-HSCT for AML in CR1 are comparable for EMBMT and EBMT. Revised version of the manuscript has been submitted for publication.

Other proposals:

- Can JACIE accreditation overcome the impact of socio-economic status and center experience on results of alloHSCT (S. Giebel, T. Czerw). For the analysis of the significance of socio-economic factors JACIE accreditation status could be included as additional variable.
- Center effect impact on outcomes after HLA matched HSCT for AML in France (S. Katsahian). There is rationale to analyze the center effect in a homogenous legislative and socio-economic environment. There is suggestion to select the patients with active disease (PIF/rel AML) where center experience may be of particular value.
- Data mining study (R. Shouval). Data mining is an alternative method for the generation of scoring systems to traditional ones e.g. logistic regression. The proposal is to use it in parallel to standard methods for evaluation of risk factors of 100 d. NRM. The study is feasible. Precise definition of the inclusion criteria is needed.

Immunotherapy Subcommittee (Leader: C. Schmid)

Ongoing studies:

- Pre-emptive or prophylactic use of DLI (A. Rank, C. Schmid). Questionnaires have been prepared and will be distributed. Centers are invited to participate in an observational study.
- Use of azacitidine after alloHCT for AML (C Craddock). The goal is to evaluate results of azacitidine treatment in patients with AML and MDS who relapsed after alloHSCT. The Cellgene funds full-time data manager to take care of the study. The study should start in Dec 2012.
- Sequential Chemotherapy Followed by RIC allo-SCT in Adult Patients with Relapsed or Refractory AML (O. Ringden). Retrospective comparison of FLAMSA followed by BuCy vs. TBI/Cy shows no differences. There is suggestion to do analyze it in various age groups.

- Long-term results after second transplant for relapsed AML (G. Andreola). The probability of OS at 10 years after 2nd alloHSCT is 10%. Factors associated with better outcome are CR at 2nd HSCT, interval between 1st and 2nd alloHSCT >10 months, the use of TBI.

Other proposals:

- The GVL effect in HLA-identical siblings and MUD using RIC as opposed to MAC (O. Ringden). It is hypothesized that GVL effect may be stronger after RIC vs. MAC-alloHSCT. Relapse rates and LFS according to the incidence of acute and chronic GVHD will be studied.
- Strategies to treat relapse after haploidentical SCT (F Ciceri). The identification of "true" haploidentical transplants (2 antigen mismatched familiy donors, in contrast to mismatched family donors with only one disparity) within the registry is ongoing. Based on this, the proposal will be further developed.
- Second transplant in the MUD setting (G. Andreola). Feasibility has been checked; a questionnaire will be prepared.

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

Ongoing prospective studies:

- Randomized comparison of RIC vs. chemotherapy as post-remission therapy in elderly patients with AML (D. Niederwieser, M. Mohty). The study is ongoing. Centers interested are invited to join it. Questions regarding the regulatory issues should be addressed to prof. Dietger Niederwieser.

Ongoing studies:

- Correlation of number of consolidation courses and outcome after RIC allo-SCT for AML (M. Yeshurun). Interpretation of the results is difficult due to unknown reasons for not administration or administration of various numbers of consolidation cycles prior to alloHSCT. The pre-selection bias related to various interval from CR to HSCT should also be properly addressed.
- Comparison of FB2 versus FB4 in alloHSCT for AML in CR1 (M. Kharfan-Dabaja, M. Mohty). Analysis has been done and the results will be presented during the ASH meeting 2012 as a poster.
- Significance of Busulfan Dose Intensity On Outcomes of Hematopoietic Cell Allografting for AML in Second Complete Remission or Beyond (A. Bzarbachi, M. Kharfan-Dabaja, M. Mohty). Analysis has been done and results will be presented during the ASH meeting 2012 as a poster.
- Effect of conditioning intensity on outcome of AML with monosomal karyotype transplanted in CR1 in patients over 50 year-old (X. Poiré). The study can be performed without additional data collection. Secondary AML should be included.

Other proposals:

- Impact of conditioning intensity on outcome of AML patients with AlloSCT in CR1 age 40-60 (J. Passweg). According to initial analysis results of RIC and MAC URD-HSCT appear comparable.
- Impact of dose intensity in RIC allo-SCT for ALL: a joint EBMT and CIBMTR study (M. De Lima, R. Ashley, M. Mohty). The study is of high scientific value. Cooperation with CIBMTR is needed.

Molecular Markers Subcommittee (Leader: J. Esteve)

Ongoing studies:

- Outcome of alloHSCT for AML with monosomal karyotype (M. Brands-Nijenhuis). The manuscript is in preparation.
- Impact of NPM1 & FLT3-ITD mutational status on the outcome of alloHSCT for normal cytogenetics AML (C. Schmid). The following has been suggested: to include data on CEBPA mutation status, to increase the study population, to include comparative cohort of patients treated without HSCT, derived from national cooperative study groups.
- HSCT for APL in the ATO era (J. Sanz). According to the analysis, auto- and alloHSCT provide similar results for APL in CR2.
- Outcome of alloHSCT for Ph(+)-ALL in CR1 in the era of TKIs (E. Brissot). Results of alloHSCT for ALL Ph(+) improved markedly since 2007. Additional data on pre- and post-transplant treatment with TKIs are being collected.
- Outcome of alloHSCT for T-ALL (X. Cahu). In the so far analysis the use of TBI appears the only factor associated with improved outcome in a setting of T-ALL (oral presentation during the ASH meeting 2012). However, some data are missing and are currently being collected: details of conditioning, use of ATG, immune subtypes. General discussion on the use of TBI has been raised. It may be assumed that high toxicity of the treatment postulated in the XXth century may not necessarily be the observed nowadays with improvement of the irradiation techniques. Therefore it has been decided to perform a survey on the current practice in Europe.

Other proposals:

- Outcome of alloHSCT for AML with abn(17p) (J.M. Middeke/J. Schetelig). The study is not feasible due to low number of patients.
- Outcome of alloHSCT for AML associated to 7q abnormalities (M Brands-Nijenhuis). Patients with secondary AML should be included.
- Survey on treatment with FLT3 inhibitors of relapsed FLT3-ITD AML (M. Brands-Nijenhuis). The questionnaire should include the issue of participation in clinical trials. Appropriate authorization will be needed in such a case.

Alternative Donors Subcommittee (Leader: F. Ciceri)

Ongoing studies:

- Impact of NIMA in MUD alloHSCT for AML (A. Schmidt, J. Pingel). The study is on-going. First results will be presented during the EBMT meeting 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). This is brief communication based on the registry data. Will be presented as oral communication during the ASH meeting 2012.
- Haploidentical mismatched allogeneic versus autologous HSCT in Adult Patients with AML in CR1: a pair-matched analysis (NC. Gorin). Preliminary results indicate advantage of autoHSCT over haplo-HSCT. However, results may be biased by different criteria for patient selection.
- Survey on unmanipulated graft haploidentical transplantation (F. Ciceri). Initial results have been presented. The procedure becomes more and more widely used. Hence, the number of patients should grow rapidly. Longer follow-up and more details on conditioning and AML karyotype are needed.

Other proposals:

- HLA-DP functional matching in unrelated donor SCT: proposal for a prospective study (K. Fleischhauer). The study has been proposed to select donors avoiding non-permissive HLA-DP T-cell epitope mismatches. Prospective results would be compared with historical controls.

Potential organizational difficulties have been raised including limited so far cooperation with national registries and HLA laboratories.

- Immune determinants of outcome in haploidentical transplantation (A. Bondanza). The study is of high scientific value and will be run in cooperation with Immunobiology WP. Appropriate questionnaires will be distributed.

Other proposals/studies

- CMV serostatus impact (M. Schmidt-Hieber). The manuscript is in circulation among co-authors.
- Survey on the use of Thiotepa as part of the conditioning regimen in ALL and AML (M. Mohty). The interest on Thiotepa increased with its registration for conditioning with and without TBI. Questionnaire for the survey will be prepared.
- Therapy and outcome of allogeneic transplantation in adults with ALL who have CNS involvement at diagnosis or relapse (D. Marks). The available data are not adequate for the proposed analysis.
- Outcome of patients with therapy-related myeloid neoplasms and persistent primary malignancies following allografting (H. Sill). The study is being conducted in cooperation with Chronic Leukemia WP.
- Impact of previous gemtuzumab administration in AML patients after allo-SCT (P. Chevallier). The use of gemtuzumab may increase with new publications on its utility in AML. The analysis in the context of alloHSCT is important and will be done.
- For male patients with ALL and AML, who is the best donor? (O. Ringden). The study does not require additional data collection therefore appears feasible.

List of participants:

Andreola Giovanna, Bandini Giuseppe, Baron Frédéric, Ben-Barouch Liran Sharon, Brunet Salut, Cahu Xavier, Cerretti Raffaella, Ciceri Fabio, Cornelissen Jan J, Crocchiolo Roberto, Czerw Tomasz, Essink Monika E., Esteve Jordi, Finel Hervé, Gabriel Ian, Giebel Sebastian, Giglio Fabio, Gorin Norbert Claude, Hemmati Philipp, Hopper Olaf, Itala-Remes Maija, Labopin Myriam, Laroulandie Martine, Mannone Lionel, Marie Jean Pierre, Mohty Mohamad, Moukhtari Leila, Nagler Arnon, Narni Franco, Niittyvuopio Riitta, Pavlu Jiri, Perez Requejo Isabel, Poire Xavier, Polge Emmanuelle, Rintala Hannele, Robin Valérie, Rubio Marie-thérèse, Salmenniemi Urpu, Schlenk Richard, Schmid Christoph, Sengelov Henrik , Shouval Roni, Spyridonidis Alexandro, Svahn Britt Marie, Szotkowski Tomas, Tassara Michela Giulia, Veelken J.H. , Volin Liisa, Yakoub-Agha Ibrahim, Yeshurun Moshe,

Sebastian Giebel
Secretary of the ALWP
sgiebel@io.gliwice.pl

Mohamad Mohty
Chair of the ALWP
mohamad.mohty@univ-nantes.fr