

CLWP Update for the EBMT News November 2004

Prospective Clinical Studies of the Chronic Leukaemia Working Party (CLWP)

Several prospective randomised studies are currently open or are very close to being opened, in accordance with the new EU regulations, by the different subcommittees of the CLWP, including the Multiple Myeloma (MM), Myelodysplastic syndromes (MDS), Chronic Myelogenous Leukaemia (CML) relapse, Chronic Lymphocytic Leukaemia (CLL), autologous CML and complications subcommittees:

The Multiple Myeloma subcommittee is running the following studies:

1. NMAM 2000, which in a genetic randomisation is investigating the role of **“reduced intensity conditioning stem cell transplantation (SCT) after autologous SCT in comparison to a second autologous SCT”**. The study has recruited more than 250 patients and has been extended until 31st January 2005, when the unrelated protocol will be ready. The new study which compares unrelated SCT with related SCT and with two autologous SCT is currently in the discussion phase.
2. **“A randomized controlled study of Velcade (Bortezomib) + Thalidomide + Dexamethasone compared to Thalidomide + Dexamethasone for the treatment of patients with myeloma progressing, or relapsing, after autologous transplantation”**. The combination treatment Thalidomide + Dexamethasone is currently one of the best salvage therapies and is tested against the new promising combination Velcade + Thalidomide + Dexamethasone. Patients will be treated for one year with one additional year of follow-up. The primary endpoint is time-to-progression (TTP), with the secondary endpoints being overall survival (OS), response rate (RR) and toxicity. The pharmaceutical company Johnson & Johnson is supporting the trial and will deliver Velcade free-of-charge. Further information can be obtained from Dr. Garderet, Hôpital Saint Antoine, Service d'Hématologie, 184 rue du Faubourg Saint Antoine, 75571 Paris Cedex 12, France.

3. **“Allogeneic stem cell transplantation from unrelated donors after dose-reduced intensity conditioning regimen in patients with multiple myeloma and relapse after autologous stem cell transplantation: A phase II study”**. This study is open for patient recruitment in selected European countries including Germany and to-date half the target number of patients have been enrolled.

The Myelodysplastic syndromes subcommittee has launched the following trials:

1. **Prospective phase III randomised study to evaluate the role of remission induction and consolidation prior to allogeneic SCT and to evaluate the benefit of peripheral blood (PB) versus bone marrow (BM)**. Study coordinator: P. Guardiola /T. de Witte). This is a two-by-two factorial study design (double randomisation). The patients will be randomised for PB versus BM in a 2:1 manner. The total number of patients will be 240. Study duration is envisaged for 3 years. It has already opened in the Netherlands and will be opening soon in other European countries once the requirements of the new EU regulations are satisfied.
2. **Standard versus dose-reduced conditioning followed by allogeneic stem cell transplantation in patients with Myelodysplastic syndromes (MDS) /or acute myelogenous leukaemia (AML): A prospective randomised multi-centre study**. Study coordinator: N. Kröger. The hypothesis will be reduction of non-relapse mortality from 40% after standard conditioning to 25% after dose-reduced conditioning and no difference in two years disease-free survival (DFS) between the two arms. Inclusion criteria: MDS /sAML less than 20% blasts with or without chemotherapy, including chronic myelomonocytic leukaemia (CMML) dysplastic forms. Age of patients will depend on type of donors: Human Leukocyte Antigens (HLA)-matched sibling donor: 50–65 years and matched unrelated donors: age 18-55 years. Stem cell source: peripheral blood stem cells (PBSC) preferred ($>3 \times 10^6$ CD34/kg body weight). The study will allow one standard arm for matched siblings only: Busulphan 12 mg/kg intra venous (iv) or Busulfan 16 mg/kg orally plus Cyclophosphamide 120 mg/kg and one dose-reduced arms: Busulphan 6 mg/kg iv or Busulphan 8 mg/kg orally plus fludarabine 5×30 mg/m²; 3 schedules for additional immune suppression will be allowed for unrelated donors (no additional immune suppression, -thymocyte globulin (ATG) or Campath). The ATG dosage will be

flexible: Fresenius (30-60 mg/kg) and Sangstat (6-10 mg/kg). The study is open for entry in Germany and will open in the other European countries once the requirements of the new EU regulations are satisfied.

3. **“Allogeneic stem cell transplantation after dose-reduced intensity conditioning regimen for patients with myelofibrosis with myeloid metaplasia (MMM): A phase II-study”**. This study is open for inclusion and currently half the target number of patients have been enrolled.

The Complications subcommittee is working on the following studies:

1. **“OKT-3 for treatment of steroid refractory graft versus host disease (GvHD)”**, which is a phase III study with almost 100 patients entered. The study is still open. All patients with GvHD have to be registered before low dose steroid treatment and OKT-3 support is provided by the company.
2. A very interesting study is the trial investigating the role of **“Defibrotide for the prevention of post-transplant microangiopathy”**. This is concurrently a registration study for Defibrotide. To define the complication of “post-transplant microangiopathy” a consensus process involving a large number of experts in the field was initiated and the criteria for diagnosis defined. Defibrotide will be prescribed for patients at high risk and the occurrence of post-transplant microangiopathy, the incidence of Veno-Occlusive Disease (VOD) and GvHD, will be compared between treated and untreated patients.

Activities of the CML relapse subcommittee:

This subcommittee is in charge of a **“randomized Phase III study of donor lymphocyte infusions (DLI) vs. Imatinib followed by DLI for relapse after allogeneic blood or marrow transplantation for CML”**. Molecular, cytogenetic or haematological relapses of Philadelphia positive (Ph+) CML after HLA-identical sibling (SIB) or Matched Unrelated Donor (MUD) SCT are accepted and the proportion of patients alive in molecular remission at 3 years, between the two treatment arms, is evaluated. Furthermore, the study assesses and compares the quality-of-life (QoL), GvHD, myelosuppression, response rate, duration of remission, safety profile, overall

survival and failure-free survival between the two treatment arms. The study will be conducted in approximately 30 EBMT centres. Power calculations indicate that to demonstrate a 20% difference in the primary objective between 60% (Arm A) and 80% (Arm B), 144 patients (i.e. 72 patients per arm) must be entered into the study during a period of 2 years, with a follow-up time of 3 years.

[The CLL subcommittee:](#)

The CLL subcommittee is investigating the role of **“autologous SCT in the treatment of chronic lymphocytic leukaemia”**. For this purpose, patients reaching a complete response (CR) or partial response (PR) after one or two lines of therapy are randomized to receive either no treatment or autologous SCT. In evaluating event-free survival (EFS) and overall survival (OS) from randomisation, more than 100 patients have been entered into this multinational trial. The study also is open to new centres.

Last but not least, we want to analyse the role of **“reduced intensity conditioning SCT in comparison to conventional conditioning for the treatment of chronic myelogenous leukaemia”**. This study was discussed in detail during the last CLWP meeting in Nijmegen and is of fundamental importance in the Glyvec era. Using reduced intensity conditioning a reduction in transplant related mortality (TRM) is expected. It has to be shown if this advantage is offset by an increased relapse rate. This study should answer the question regarding the optimal conditioning therapy for allogeneic stem cell transplantation in patients with CML. This study is part of the Centre of Excellence programme “LeukemiaNet” of the EU Sixth Framework Programme and involves many of the national study groups.

We would greatly appreciate your participation in these studies so please do not hesitate to ask should you require any further information. Following implementation of the European Directive on Clinical Trials the organisational burden of running studies has increased considerably, as have expenses such as insurance. Please study the proposal carefully and if you commit yourself to a study adhere to this commitment by providing written consent. The “clinical trials participation form” can be downloaded from the EBMT/CLWP webpage:

<http://www.ebmt.org/5WorkingParties/CLWP/clinical%20trials%20participation%20form.doc>

Please send all information to the EBMT CLWP Data Office Leiden by fax: (+31) 71 5276799 or email: CLWPEBMT@lumc.nl.

The next CLWP meeting will take place 14-15 January 2005 in Lyon, France. If you would like to join us please contact the organizing physician, Mauricette Michallet: Hopital E. Herriot, BMT Unit Pavillon E, 5 Place d'Arsonval, 69437 Lyon, Cedex 03, France. Tel: (+33) -4-72-11-7402, Fax: (+33) -4-72-11-7404, Email: mauricette.michallet@chu-lyon.fr.

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