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Highlights and strategies of the EORTC Leukemia Group

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Abstract

The EORTC Leukemia Group comprises more than 45 qualified haematology centres in Europe. The group promotes cooperation with new centres from Central and Eastern Europe with the aim to improve the standard and quality to the level in Western Europe. Subcommittees on cytogenetics, molecular biology, and immunology, shared by experts in the field, are active and have meetings on a twice-yearly basis. The aim of our group is to organise phase II and phase III trials for patients with acute and chronic myeloid or lymphoid leukaemia, myelodysplastic syndromes and myeloma. In 2000, 330 patients have been included in nine trials of the group. Presently, more than 2600 patients included in previous and current studies are alive and under continuous follow-up allowing studies on the long-term results to be planned. © 2002 Published by Elsevier Science Ltd.

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1. Highlights from clinical studies

1.1. Phase III studies in AML

The acute myeloid leukaemia (AML) 10 study for AML patients aged up to 60 years old was activated in 1994 and closed in 1999. This is a joint study between the EORTC Leukemia Group and the Italian GIMEMA. In this trial, three types of anthracyclines have been used in a randomised study in induction and consolidation courses. After achievement of complete remission and a high-dose consolidation course, autologous or allogeneic stem cell transplantation was planned for all patients. Those patients scheduled for autologous stem cell transplantation were randomised between a marrow and a peripheral blood stem cell transplantation. In total, 2157 patients from 75 centres have been randomised. For the second question, almost 300 patients have been randomised. The study has been presented on several occasions at international meetings. Major improvements were obtained over the last 25 years, along with an increased intensity of the induction–consolidation treatment and the inclusion of stem cell transplantation as a post-consolidation treatment in our AML trials for patients younger than 60 years (Fig. 1) [1–7]. Dr Susan Keating defended her PhD thesis in Nijmegen, The Netherlands on 22 October 1999, based on the scientific work she performed on the AML studies at the Data Center in Brussels [8–10]. S. Suciu presented the prognostic importance of cytogenetic characteristics and the outcome comparison of autologous and allogeneic stem cell transplantation based on the intent-to-treat principle [11], and T. de Witte presented the results of the randomisation between autologous marrow and peripheral blood transplantation at the ASH meeting in Orlando, USA, December 2001.

In 1996, the AML-13 trial comprising patients over the age of 60 years has been initiated. The effect of granulocyte-colony stimulating factor (G-CSF) on the remission induction rate and the duration of remission has been studied in a randomised manner. A second randomisation has been performed in those in complete remission to study the question of a consolidation course in the hospital or a similar consolidation course to be given outside the hospital using intravenous (i.v.) or oral idarubicin, respectively. The study has been closed in March 2001 and 722 patients have been registered. A total of 346 patients have been randomised for the second question. The first analysis will be performed in December 2001. The overall results are comparable with those of the previous EORTC LG studies in elderly

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AML patients, which were conducted in collaboration with or without the HOVON or GIMEMA groups [12–14].

Subsequently, a phase II trial AML-15/P over the age of 60 years has been initiated. This trial aims to assess the feasibility, toxicity and antileukaemic activity of Mylotarg® (anti-CD33 + calicheamycin) as a front-line therapy in elderly patients with previously untreated AML. S. Amadori presented an interim analysis at the ASH meeting in 2001.

1.2. Myelodysplastic syndromes

For patients with so-called 'high risk' myelodysplasia and secondary AML under the age of 60 years, a trial (06961) was initiated in December 1996. The induction of remission is performed with combination of idarubicin, Ara-C and etoposide. After achievement of a complete remission, a consolidation follows using intermediate doses Ara-C and idarubicin. When the patient is still in remission and an allogeneic donor is not available, a randomisation follows comparing peripheral blood stem cell transplantation and a second consolidation with high dose Ara-C. The accrual is ±60 patients per year from 31 centres. As of December 2001, 308 patients have been registered, and 66 have been randomised for the second question. A Biomed grant (CRIANT) has been acquired to study Europewide the molecular follow-up in these patients. J. van Dijk, a research fellow, presented an interim analysis of the impact of a cytogenetic or polyclonal remission on treatment outcome at the ASH meeting in 2001. The study will continue until 100 patients have been randomised for the post-consolidation question. The overall results of the current study are in line with the ones of the previous study (06921), recently published in *Blood* [15]. They were superior to the ones of the very first study (06888), where chemotherapy alone was administered [16].

1.3. Acute lymphoblastic leukaemia

For acute lymphoblastic leukaemia, the ALL-4 trial, successor of the ALL-1 [17], ALL-2 [18] and ALL-3 studies, has been initiated in 1995. This trial compares the effects of prednisone versus dexamethasone in the remission induction phase and in the consolidation phase. A second randomisation compares continuous intensive maintenance chemotherapy courses versus autologous stem cell transplantation followed by low dose maintenance courses. The second question is similar to the one addressed by the French LALA group. An intergroup study for patients with bcr/abl-positive ALL in collaboration with GIMEMA and the French LALA group has been very successful thus far. These three groups registered a total of 231 patients. The final analysis has been performed, and a paper is in preparation.

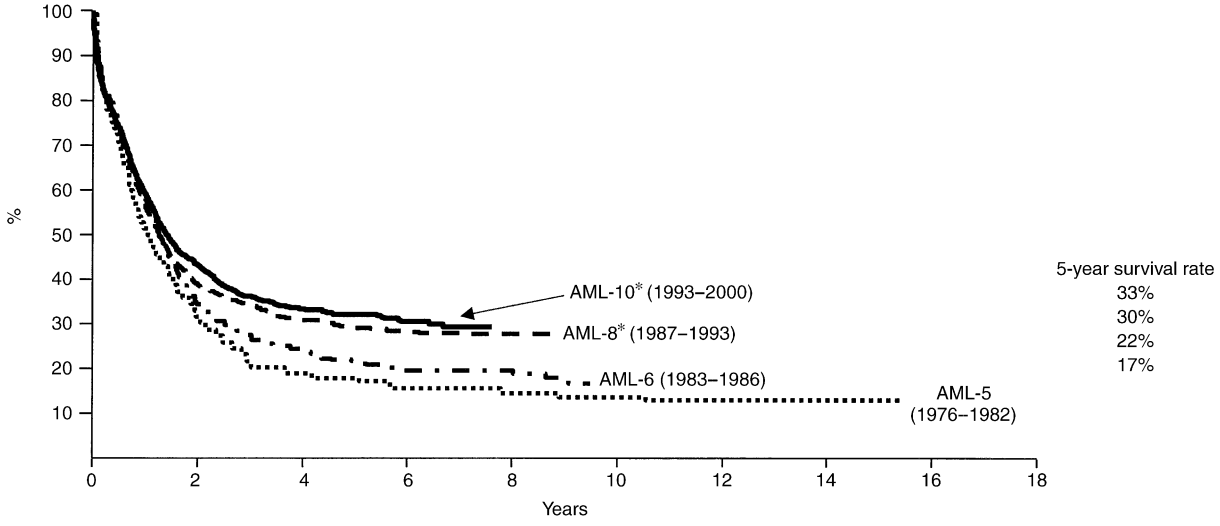

Fig. 1. Duration of survival in four consecutive studies of the EORTC Leukemia Group in AML patients younger than 60 years. *In collaboration with the Italian GIMEMA Group. O, observed; N, number; AML, acute myeloid leukaemia.

1.4. Chronic lymphocytic leukaemia

The randomised phase II study on the effect of high dose chlorambucil versus fludarabine in previous untreated progressive B-CLL has been finalised. 88 patients were randomised by 16 centres. A new randomised phase III study 06992 (CLL-3) comparing low dose chlorambucil maintenance versus no-maintenance in CLL patients with a good partial or complete remission after high-dose chlorambucil induction has just been opened to patient entry.

2. General strategy of the EORTC Leukemia Group

The aim of our group is to organise phase II and phase III trials for patients with acute and chronic myeloid and lymphoid leukaemia, myelodysplastic syndromes and myeloma. The clinical trials are to be supported by translational studies organised by the scientific subcommittees. Recently, the group decided to establish a minimal residual disease (MRD) task force with the aim of developing strategies to monitor MRD by immunophenotyping and flow cytometry. The coordinator of this task force will be Dr Drago Baticnic, from Zagreb, Croatia.

3. Strategies in AML

The AML 10 study for AML patients up until the age of 60 years was activated in 1994 and closed in 1999. At present, we analyse the data with the aim to detect prognostic subgroups based on the presence of certain cytogenetic characteristics, and immunological or molecular features. For this aim, the molecular task force plays a crucial role. These retrospective analyses have identified prognostic subgroups leading to risk-adapted treatment in the recently developed AML-12 protocol. Ongoing analyses will identify new subgroups. A typical example is the recently identified FLT-3 internal duplication which is associated with a very poor prognosis of patients formerly considered as standard-risk patients.

The new protocol (AML-12) includes a randomisation at diagnosis for a remission induction using high dose Ara-C compared with the 'best' remission induction schedule of the AML-10 trial. After reaching complete remission, patients are treated by intensive consolidation and autologous peripheral blood stem cell transplantation. A second randomisation evaluates the value of maintenance therapy with low dose subcutaneous interleukin-2 versus no further treatment. Patients with an HLA identical family donor are scheduled for allogeneic transplantation. Poor risk patients without a sibling donor are also candidates for unrelated donor transplantation. A recently formed EORTC/GIMEMA molecular network of laboratories in The Netherlands, Belgium, France and Italy will coordinate and perform the monitoring of minimal residual disease using molecular techniques that are implemented by Dr Joop Jansen and Dr Francesco LoCoco.

Phase II studies are developed for second-line treatment of AML. A randomisation of Nestra (a farnesyltransferase inhibitor) versus no treatment will be evaluated in patients in second remission who are not candidates for transplantation.

A phase II trial AML-15/P for patients over the age of 60 years has started in 2001. This trial aims to assess the feasibility, toxicity and antileukaemic activity of Mylotarg® (anti-CD33 + calicheamycin) as a front-line therapy in elderly patients with previously untreated AML. This is the first trial of immune-targeted therapy in acute myeloid leukaemia. The group changed its strategy and subdivided elderly patients with AML into two groups: fit patients younger 70 years of age and frail patients (older than 70 years or between 60 and 70 years with comorbidity). The first interim analysis in the fit patients showed promising data. This schedule, Mylotarg followed by standard chemotherapy, will form the basis of a planned randomised study comparing standard chemotherapy and Mylotarg followed by standard chemotherapy (coordinator: Prof. Sergio Amadori).

All AML trials are joint ventures between the Italian Leukemia Group, GIMEMA, and the EORTC Leukemia Group. In this way, it is possible to perform AML studies in about 600 patients per year.

4. Strategies in myelodysplastic syndromes

For patients with so-called low-risk myelodysplasia, new phase II studies are being developed using the biology of MDS as a target. Infliximab, a tumour necrosis factor (TNF)-alpha receptor antagonist will be tested in a small phase II study. Plans for treatment with farnesyltransferase inhibitors and angiogenesis inhibitors are being developed.

The ongoing Criant trial (06961) was initiated in December 1996. So far, 308 patients have been registered, and 66 patients have been randomised for the comparison of intensive consolidation versus ASCT. The Biomed grant (CRIANT) facilitates the translational molecular studies in this trial. Further follow-up and more patients will allow an analysis of the impact of cytogenetically normal, polyclonal remission. Phase II studies are currently being developed to explore the possibilities of incorporating Mylotarg in the treatment schedules for these patients.

A new protocol with the DNA demethylating agent, decitabine, has been developed for high-risk MDS patients over the age of 60 years. The value of decitabine in this older patient group will be compared with standard supportive care.

Table 1
Current members of the Leukemia Group

City	Hospital	Physician
Belgium		
Brussels	Institut Jules Bordet	Dr Bron
Brugge	Academisch Ziekenhuis St. Jan	Dr Selleslag
Antwerpen	Algemeen Ziekenhuis Middelheim	Dr De Bock
Antwerpen	Universitair Ziekenhuis Antwerpen	Pr Berneman
Verviers	Centre Hospitalier Peltzer—La Tourelle	Dr Vermeulen
Brussels	Clinique Universitaire St Luc	Pr Ferrant
Brussels	Hopital Universitaire Erasme	Pr Feremans
Liège	CHR de la Citadelle	Dr De Prijck
Leuven	U.Z. Gasthuisberg	Pr Boogaerts
Liège	CHU Sart-Tilman	Dr Fillet
Charleroi	CH Notre-Dame	Dr André
France		
Nice	Centre Antoine Lacassagne	Pr Thyss
Villejuif	Institut Gustave Roussy	Dr Bourhis
Lyon	Hopital Edouard Herriot	Pr Fière
Paris	Hotel-Dieu de Paris	Pr Marie
Paris	Hopital Cochin	Pr Dreyfus
Paris	Hopital Necker	Pr Varet
Macon	Centre Hospitalier de Macon	Dr Belhabri
The Netherlands		
Den Bosch	Groot Ziekengasthuis	Dr Sinnige
Veldhoven	St. Josef Ziekenhuis	Dr Vreugdenhil
Rotterdam	Rotterdan Cancer Institute	Pr Lowenberg
Nijmegen	St. Radboud University Hospital	Pr de Witte/Dr Muus
Amsterdam	Onze Lieve Vrouw Gasthuis	Dr Roozendaal
Leiden	Academisch Ziekenhuis Leiden	Pr Willemze
Maastricht	Academisch Ziekenhuis Maastricht	Dr Schouten
Den Haag	Leyenburg Ziekenhuis	Dr Wijermans
Rotterdam	Erasmus Universiteit	Dr Sonneveld
Switzerland		
Basel	Kantonsspital Basel	Dr Gratwohl
Germany		
Heidelberg	Ruprecht Karls universiteit	Dr Ho
Muenchen	Klinikum Grosshadern Ludwig-Maximilians Univ. Muenchen	Prs Hiddemann/Jehn
Tuebingen	Eberhard Karls Universitaet	Dr Denzlinger
Herrsching	Medizinische Kinink Schindlbeek	Dr Dietzfelbinger
Italy		
Reggio Calabria	Ospedali Riuniti	Pr Nobile
Rome	Ospedale San Eugenio	Pr Amadori
Rome	Policlinico Umberto Primo—University La Sapienza	Pr Mandelli/Dr Meloni
Rome	Policlinico A. Gemelli	Pr Leone
Bolzano	Ospedale Generale Regionale	Pr Coser
Portugal		
Porto	Hospital Escolar San Joao	Dr Ribeiro
Coimbra	Hospitalis Da Universidade De Coimbra	Dr Sousa
Austria		
Innsbruck	Innsbruck Universitaetsklinik	Drs Gastl/Stauder/
Zwierzina		
Hall-In-Tyrol	Bezirkskrankenhaus	Pr Schmalzl
Croatia		
Zagreb	Clinical Hospital Rebro	Pr Labar
Zagreb	O Novosel Medical School	Pr Jaksic
Czech Republic		
Prague	Instit. Hematology	Dr Cermak
Prague	Charles University	Drs Kvasnicka/Neuwirtova
Olomouc	University Hospital	Pr Indrak

(continued)

Table 1 (*continued*)

City	Hospital	Physician
Turkey		
Ankara	Ibni Sina Hospital	Pr Beksac
Hungary		
Budapest	St. Lazlo Hospital	Dr Fekete
Szeged	Szent Gyorgyi Medical School	Dr Borbenyi
Kaposvar	County Hospital	Dr Egyed
Slovakia		
Bratislava	University Hospital	Dr Mistrik
Macedonia		
Skopje	Medical Faculty	Dr Cevreska

5. Strategies in acute and chronic lymphoblastic leukaemia

A new trial with randomisation of STI 571 (Glivec) in combination with chemotherapy during consolidation is planned in Ph-positive ALL. A new study in elderly Ph-positive ALL (with STI 571) is planned in Cupertino with the French LALA-group. A new ALL-5 trial is in preparation. This study will be developed in Cupertino with the GIMEMA. Patients in this study will be particularly stratified for risk-adapted treatment, mainly according to immunological criteria. The initial randomisation will ask the question of intensification during induction (+Campath, +HD anthracycline, +HD Ara-C).

A new randomised phase III study 06992 (CLL-3) comparing low-dose chlorambucil maintenance versus no-maintenance in CLL patients with a good partial or complete remission after high-dose chlorambucil induction has been opened to patient entry in March 2001. The first patient has been entered in August 2001.

6. Strategies in quality assurance

Quality assurance is mainly based on the review of patients for eligibility and evaluability performed by the study coordinators along with the methodological approach of the Leukemia Unit according to the EORTC Data Center quality assurance procedures. Independent review of cytology, cytogenetics, molecular biology and immunology by four subcommittees, and occasional site visits to participating centres have led to improvements in the quality of the studies of the Group.

7. Collaboration with other groups

The Leukemia Group has a very close relationship with the Italian GIMEMA Group. Many clinical studies are joint studies. This combination is very advantageous for both groups since this intergroup forms the largest group for leukaemia treatment research in the world. Our Group also has regular contacts with the EORTC Children Leukemia Group and the EORTC Lymphoma Group. There are also joint studies with the French LALA Group and the European Blood and Bone Marrow Transplantation Group.

The EORTC Leukemia Group is a member of the AML Collaborative Group, which comprises all cooperative groups performing randomised trials and AML in collaboration with the MRC and HOVON. The EORTC/GIMEMA plays a major role in conducting meta-analyses with the support of a Biomed grant.

Acknowledgements

Pierre Stryckmans was one of the inceptors of the Hemopathies Working Party of the EORTC in 1971. He coordinated the successive ALL and CML trials and had been a former chairman of the Leukemia Group. He passed away in July 2001 and the Leukemia Group is very thankful for this commitment. Both Professors Marcel Hayat and Robert Zittoun have retired. They were coordinators of the AML-5 trial and of the AML-6, AML-8 and AML-10 trials, respectively. Robert has also been former chairman of the Leukemia Group, and developed the Quality of Life studies in our Group. The achievements of the Leukemia Group would not have been possible without the involvement and contribution of our data managers, Gabriel Solbu, Murielle Dardenne, Peggy Rodts, Filip Beeldens and Goedele Eeckhout, and of the laboratory researchers who are in charge of the cytology, cytogenetics, immunology and molecular biological studies, Franz Schmalzl, Monique Cadiou, Anne Hagemeijer, Alain Bernheim, Shama Bhola, Michel Bernier, Toon Smetsers, Job Janssen and Elizabeth MacIntire.

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