The EORTC Children’s Leukemia Group: Preclinical and clinical research and resulting achievements

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ABSTRACT

The EORTC Children’s Leukemia Group (CLG) is a spin-off from the EORTC Hemopathies Working Party (adults and children). After a decade of collaboration in the adult-pediatric group it became clear that there was not only a large difference in cure rates between children and adults, but many chemotherapeutic-toxic borders were substantially different. During the following decade the CLG was not only a witness of a very exciting battle against childhood leukemia, but it also contributed substantially to better cure rates for these diseases.

The main activity of the CLG was concentrated on the field of acute lymphoblastic leukemia (ALL). Fine tuning of treatment elements using the BFM design as a backbone has been done very successfully over the past decades. The CLG has many achievements, and the major ones include: the 58831 trial showing the superfluity of the prophylactic Central Nervous System (CNS) radiotherapy in ALL patients when adequate systemic and CNS directed chemotherapy is ascertained. The 58881 trial demonstrated that the assessment of minimal residual disease (MRD) at completion of induction in ALL is a key step in the process to categorizing and allocating patients into different risk groups, and that MRD is a powerful and independent prognostic factor. This same 58881 trial showed the clear difference in efficacy of different...
1. History of the EORTC Children’s Leukemia Group (CLG)

Among all types of childhood cancers, leukemias and lymphomas account for approximately 40% of the cases. The most common subtype of leukemia in children is acute lymphoblastic leukemia (ALL), and the lymphoblastic origin is also prominent in non-Hodgkin lymphomas (NHL) of childhood.

Survival has increased for all childhood cancers since the late 1960s, but by varying amounts and at different points in time. The most spectacular improvement in the recent 50 years has been seen in the cure rate of the lymphoblastic malignancies (leukemia and lymphoma). For childhood ALL, overall survival (OS) rates were less than 5% before 1970 but nowadays with contemporary risk-directed therapy have reached a 5-year Event-Free Survival (EFS) and OS of 80–85% and 90%, respectively.1,2 Also in childhood NHL the cure rates have risen dramatically to reach a 5-year OS rate of 90%. These improvements are not linked to more effective drugs but rather to the accurate use of already existing drugs (effective combinations), to an improved understanding of the natural behavior of the disease (sanctuaries protecting cancer cells), to the fine-tuning of delivering chemotherapeutic interventions (late intensification, maintenance), and to a better identification of prognostic factors. The use of stem cell transplantation has also improved the outcome of these young patients with very high risk features.

The EORTC Children’s Leukemia Group (CLG) is a spin-off from the EORTC Hemopathies Working Party (adults and children) and has been right in the middle of the exciting battle against this childhood cancer. The Hemopathies Working Party started its activities in 1971. Between 1971 and 1978, patients from Belgian and French centers were registered in the first ALL trial 58741. This study evaluated in particular two types of consolidation therapy (polychemotherapy versus a methotrexate-based consolidation therapy) and two types of maintenance therapy (chemotherapy versus immunotherapy). Especially the inferiority of the immunotherapy as maintenance therapy was striking.3

Another important conclusion of this study was the large difference in EFS and OS of children and adults. In the beginning of the 1980’s, very promising results asparaginases resulting in an optimization of the use these drugs and a revival of interest for the asparaginases in the treatment of ALL.

In the near future the CLG will focus mainly on translational research projects and innovative biologically targeted treatment approaches, on collaborations with other children’s leukemia groups in intergroup studies, and on the evaluation of the long-term outcome of childhood cancer survivors.

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treatment in pediatric ALL-regimens. Three asparaginase preparations are available: the native asparaginase derived from Escherichia coli (E. coli asparaginase), a product isolated from Erwinia chrysanthemi (i.e., Erwinia asparaginase) and a pegylated form of the E. coli enzyme (PEG-asparaginase). Only in the last decade has the importance of asparaginase in the treatment of ALL become clear, and it is now believed to be a cornerstone of treatment protocols for ALL. Most clinical evidence in the use of asparaginase is based on non-randomized trials. More than 20 years ago, it was suggested that there was a similar efficacy between native E. coli asparaginase and Erwinia asparaginase, with a less toxic pattern for the E. chrysanthemi formulation.

In 1988 the CLG started a trial using a BFM-like protocol and compared the efficacy and toxicity of E. coli asparaginase (E coli-Asp) versus Erwinia asparaginase (Erwinia-Asp) in a randomized fashion in children with ALL and NHL. A total of twelve doses of 10,000 IU/m² each were planned: eight during induction (protocol IA) and four during reinduction (protocol II). Between November 1990 and October 1993, 700 patients were randomized in this trial: 354 in the E coli-Asp arm and 346 in the Erwinia-Asp arm. A similar number of patients in both groups received all the planned doses during protocols IA and II. Coagulation abnormalities were more often observed in the E coli-Asp arm at induction: 30.2% versus 11.8%; odds ratio, 3.20; P < 0.0001. The incidence of other toxicities was similar in the two treatment groups. In the Erwinia-Asp arm, more patients failed to achieve complete remission after completion of protocol IA (4.9% versus 2.0%; P = 0.04) and the relapse rate was higher, leading to shorter EFS (hazard ratio, 1.59; 95% confidence interval, 1.23–2.06; P = 0.0004). The estimate of EFS rate at 6 years was 59.8% (standard error [SE] = 2.6%) versus 73.4% (SE = 2.4%). OS rate at 6 years was also lower in the Erwinia-Asp arm at 75.1% (SE = 2.3%) versus 83.9% (SE = 2.0%), P = 0.002.

This trial was the first to demonstrate the superior clinical efficacy of E coli-Asp versus Erwinia-Asp during induction and reinduction in a randomized fashion and established the basis for subsequent studies. As a result of this, E coli-Asp has become a universal component of ALL therapy and is used in every pediatric regimen for ALL. Moreover, the clinical results observed here revealed a positive correlation with laboratory-based studies conducted by other groups, confirming the important relevance of these achievements.

More recently it also became clear that clinical hypersensitivity reactions and silent inactivation due to antibodies against E coli-Asp lead to inactivation of E coli-Asp in up to 60% of cases. Typically, patients exhibiting sensitivity to one formulation of asparaginase are switched to another to ensure they receive the most efficacious treatment regimen possible.

Erwinia-Asp is now used only as a second- or third-line treatment in European and US protocols. Nevertheless, Erwinia-Asp still plays an important role in those patients unable to tolerate native forms of asparaginase and significantly contributes to the good results obtained in this group of patients. New formulations of this drug, such as the pegylated form of Erwinia, are already under preclinical study and may have a potential role in the coming years. PEG-Asparaginase is on its way to become the asparaginase of choice. Its potential benefits compared to the native E coli are very promising. Current randomized trials are aiming to answer this question in the first-line treatments.

2.2. Clinical significance of minimal residual disease (MRD) in childhood ALL: Results of the phase III EORTC 58881 trial – H. Cavé et al., 1998

Evaluation of response to treatment in children with ALL has classically been performed based on morphological findings. The extent of clearance of leukemic cells from the blood or bone marrow is an independent prognostic factor in ALL. In an attempt to go beyond the limits of the microscope, biologists and hematologists in the 1990’s developed new techniques able to identify traces of disease that escaped the accuracy of the human eye. The CLG prospectively assessed the prognostic value of the amount of detectable residual disease at several time points during the first six months after complete morphological remission of childhood ALL had been induced.

A total of 246 patients with ALL enrolled in the EORTC 58881 trial. Rearrangements of the T-cell receptor genes TCRγ and TCRδ or those for the gene for immunoglobulin heavy chain (IgH) were characterized at the time of diagnosis. A competitive PCR assay was used to quantitate the residual blasts. Two reference laboratories centralized the samples for study. Of the 246 patients, 178 (72%) were monitored for residual disease. These 178 patients were similar to the 654 patients in the non-participating centers included in the trial regarding prognostic factors and duration of remission. Median follow up was 38 months. The presence or absence (<10⁻²) and level of residual leukemia were significantly correlated with the risk of early relapse at each of the times studied (P < 0.001). PCR measurements identified patients at very high risk for relapse after the completion of induction therapy (those with ≥10⁻² residual blasts per 2×10⁹ mononuclear bone marrow cells have a risk of relapse 16 times higher than those with <10⁻² residual blasts) or at later time points (those with ≥10⁻³ have a risk of relapse 15–22 times higher than those with <10⁻³ residual blasts). Multivariate analysis confirmed that presence/absence and level of residual disease were the most powerful independent prognostic factors.
Presence of MRD was found to have a negative impact on duration of remission and OS in patients who, morphologically, reached complete remission. Patients who did not completely clear the disease after induction or later in the treatment did significantly worse than those responding to conventional therapy. Nowadays, MRD evaluation is a key step in the early process to categorize and allocate patients into different risk groups. MRD analysis was an important step forward to a more personalized medicine, clearly identifying those patients who could benefit from a more intense treatment. In the subsequent EORTC ALL trial (58951), those with a high level of MRD \( \geq 10^{-2} \) at end of induction were switched to a very high risk protocol leading to better results in terms of EFS and OS.

2.3. Comparison of high-dose methotrexate (MTX) +/- subsequent central nervous system (CNS) irradiation to prevent CNS relapse in medium and high risk patients with ALL: results of the phase III EORTC 58831/2 trials – E. Vilmer et al., 2000

Treatment for ALL must take into account the possible leukemic attenuation of the so-called sanctuary disease sites like CNS and testes. Although only 3% of children with ALL have evidence of leukemia in the central nervous system at the time of diagnosis, leukemia will become evident in this region in 50–70% of children who don’t receive prophylactic or preventive treatment. Treatment and clinical control of CNS leukemia has always been a therapeutic challenge in childhood ALL. For more than four decades, CNS irradiation has been successfully used in children with ALL as part of a multimodal treatment in order to treat and prevent the recurrence of the disease in the CNS. Cranial irradiation is indeed a very effective form of CNS-directed therapy, but its efficacy is offset by substantial rates of secondary neoplasms, endocrinopathy, neurocognitive dysfunction, and neurotoxicity. These deleterious side effects and long-term neurological deficits observed in the survivors prompted all investigators to find other ways to reduce the risk of CNS relapse and avoid the use of radiotherapy.

The CLG assessed whether the deletion of CNS irradiation in medium and high risk ALL patients receiving systemic high doses of MTX may be done without compromising the therapeutic results. Medium- and high-risk ALL patients were randomized into two groups to receive four high doses of MTX (2.5mg/m²) during induction and consolidation given concomitantly with intrathecal MTX with or without subsequent cranial radiotherapy (age adapted doses). Standard-risk patients also received four doses of MTX as prophylaxis for CNS relapse, at a lower dosage (0.5mg/m²), and no cranial irradiation. A total of 735 eligible patients, standard or medium–high risk, were included in the analysis. Of those, 183 medium- or high-risk patients were randomized for the question. High-dose MTX alone was as effective as high-dose MTX followed by cranial radiotherapy in terms of disease-free survival (DFS), isolated CNS relapse rate and isolated or combined CNS relapse rate. The 6-year DFS rates were 68% (without irradiation arm) and 66% (with irradiation arm). The isolated CNS relapse rates were respectively 7% and 7% in those without and with cranial irradiation and the CNS relapse rates were respectively 9% and 15%. For the later endpoint, the estimated hazard ratio (with irradiation versus without irradiation: control group) was 0.57, its 95% confidence interval was 0.24–1.35, which does not include 2.12 [hazard ratio corresponding to an increase in CNS relapse rate at six years from 10% (with irradiation) to 20% (without irradiation)].

The results of this study showed that CNS radiotherapy could be safely spared in these groups of patients when replaced by adequate systemic and CNS-directed chemotherapy. Since then, EORTC trials 58881 and 58951 omitted CNS irradiation successfully even in patients at high risk of CNS relapse. Hence, most contemporary pediatric protocols limit the use of this treatment modality to patients who are at particularly high risk for CNS relapse, but there is a clear tendency for most groups to move in the same direction (no radiotherapy) which has been taken by the CLG since 1988. Children with ALL can now be cured with a high rate of success and avoid the undesirable acute and long-term side effects of CNS radiotherapy (especially secondary neoplasm, endocrine and neurocognitive disorders).

3. The future of the CLG

The current rates for cure in pediatric ALL are high. Most of the pediatric hemato-oncologists experience that the limits of chemotherapeutical treatment seem to have been reached in many children suffering from ALL. Optimal use of the antileukemic agents, molecular genetic analyses of leukemic cells, pharmacodynamic studies of drugs, pharmacogenetic studies of the host’s drug-metabolizing enzymes, drug transporters, and drug targets are however providing a rational and scientific basis for further improvement of treatment efficacy as well as for the reduction of complications. Also early treatment response, as defined by the measurement of minimal residual disease, which reflects both the drug responsiveness of leukemic cells and host pharmacodynamics/pharmacogenomics, is the very reliable prognostic indicator for gauging the intensity of treatment.

3.1. Translational research (TR)

Although impressive high cure rates have been achieved in pediatric cancer treatment, there is still controversy
about the optimal treatment strategy for childhood ALL, especially regarding the risk-directed therapy. The aims of the risk-directed therapy are to avoid overtreatment for children with good prognosis, in order to reduce as much as possible the acute and the long-term toxicity, and to give more intensive therapy for children with worse prognosis. Nevertheless, with the currently used prognostic factors, there is still a risk for patients with good prognosis to be overtreated and for patients with bad prognosis to be undertreated. Further prognostic factors refining the risk-group classification should therefore be looked for. Statistical evaluation of cytogenetic, molecular, immunological, and MRD data, which have been collected prospectively in the framework of the large EORTC 58951 trial, will be done in the near future, once the randomized questions of this study (value of dexamethasone versus prednisone in induction and of prolonged versus conventional duration of E coli-Asp therapy during consolidation and late intensification) will be assessed. In addition, innovative biologically targeted treatment approaches are needed for patients with high risk criteria and for those with refractory or relapsed disease.

A better understanding of the ALL biology is thus needed and will help to identify refined prognostic factors and to develop novel molecular and cellular therapeutic strategies.\textsuperscript{19−22} This can be reached by centralizing the collection of clinical data in parallel with sampling and processing and storing biological samples according to well-defined standard operating procedures (biobanking). This centralized procedure will allow the storage of a large number of quality-controlled biological samples and the collection of relevant associated clinical data. The standardized and large collection of biological and clinical data will also give the possibility to develop well-designed TR projects, even for small ALL subgroups, the results of which will allow the design of new clinical and biological research projects.

Applied biosciences using advanced biochemical, genetic, and immunological knowledge is a very rapidly moving field. Technologies such as transcript profiling or genome-wide analyses on microarray are now broadly used in TR and require DNA and/or RNA prepared according to convenient and standardized technical procedures. Therefore, samples already banked are not always suitable for all studies. This problem is clearly illustrated by miRNA studies (extraction procedures are needed that keep small-sized RNA). For patients with newly diagnosed disease, the major trends in the coming years are to further adapt the therapy based on better defined prognostic/predictive factors.

In this context, we started a prospective biobanking study (EORTC trial 58081) with associated important TR projects. Through a better understanding of molecular mechanisms underlying leukemogenesis, they will allow further identification of new biomarkers, definition of specific subgroups within ALL, and the development of targeted therapies. This will help to prepare future biology-based randomized questions specifically oriented to particular subgroups.

3.2. Collaborations with other children leukemia groups in Intergroup studies

In Europe, most cooperative groups for the treatment of acute leukemia in children are organized on a national basis. The CLG, albeit presently in French, Belgian and Portuguese centers, is open to pediatric hematol- oncology centers or Groups from all countries and it also favors increased collaborations with other Groups. Since the EU directives have changed the conduct of clinical research trials in Europe, the role of the CLG in coordinating international studies can become more important as a result of the knowledge and experience of EORTC Headquarters in this domain.

The CLG was one of the founding members of the international ALL 1-BFM-SG (International BFM Study Group) and of the Ponte di Legno Group working group. These collaborations have led to substantial progress in leukemia research. By pooling data from all major study groups, it has been possible to improve the understanding of the biology and heterogeneity of subtypes of the disease and to acquire insight into their optimal therapy.\textsuperscript{23−25} The collaboration has mainly focused on small subgroups of ALL patients: Philadelphia-chromosome positive,\textsuperscript{26} infants,\textsuperscript{27} induction failures, hypodiploidy,\textsuperscript{28} t(4;11),\textsuperscript{29} iAMP21, t(17;19), Down Syndrome (each one 1−4% of the whole group). In these small subgroups, recommendations or clinical trials can only be launched in a large intergroup study. The CLG has contributed also to overviews performed in the framework of the Children ALL Collaborative Group by the Oxford team, on the value of cranial radiotherapy, additional treatment during induction−consolidation, and additional treatment (e.g. pulses) in maintenance.\textsuperscript{30}

3.3. Long-term outcome of childhood cancer survivors

As cure rates in ALL and NHL improve, more children experience late toxicity from their therapy, sometimes leading to late excess mortality. The increasing number of survivors has prompted studies of the long-term health consequences of treatments for childhood cancer. It is clear that damage to the organ systems of children caused by chemotherapy and radiation therapy may not become clinically evident for many years.

The most common late toxic effects are cardiotoxicity, growth retardation, obesity, endocrine disorders, fertility impairment, central nervous system effects, and secondary neoplasms. Assessment of the long-term survival of children cured of cancer must consider also their
social outcome. Age at diagnosis, sex, current age, socio-economic status, and life transitions may affect social outcome of childhood cancer survivors. The treatment type or intensity may also affect psychosocial functions. Based on the large CLG experience we have the opportunity to analyze a large series of childhood ALL and NHL survivors with long-term follow up and treated according to well-defined protocols. It will also allow comparisons between treatment arms (e.g. with or without cranial radiotherapy) and risk groups. A better knowledge of the long-term follow up and the late adverse events is indeed essential in view of the improvements of cure rates. This would be useful in order to set up a specific and standardized long-term follow up for patients treated for childhood ALL and NHL in EORTC studies. It would also help to further adapt therapy in order to avoid overtreatment of low-risk patients and therefore reduce as much as possible the occurrence of late effects in this population.

4. Acknowledgements

The achievements of the CLG would not have been possible without the involvement and contribution of many. First of all we have to thank the patients and their families who agreed to take part in our clinical research trials. Thanks to their ability to cooperate in clinical trials, we were able to make further progress in the research and treatment of these diseases.

Without the huge efforts of many clinicians who work or have worked in the participating centres we could never build up such a nice experience.

In many ways J. Otten (Brussels) has been the key player for the CLG. He was not only at the cradle of the Group, he has also been the driving force of our clinical research group during many years. His outstanding scientific input has substantially contributed to many important CLG achievements.

The Group is also very grateful to N. Philippe† (Lyon), founder-member and also the first president of the Group, A. Boilletot (Strasbourg) founder-member and past-president and E. Vilmer† (Paris) past-president who carried our Group with great success in the era of translational research.

We also honor here our late founder-members: P. Strijckmans† (Brussels) and M.J. Delbeke† (Gent) and our retired colleagues: M. Casteels-Vandaele (Leuven), C. Behar (Reims), R. Maurus (Brussels), J.M. Chantraine (Liège), J. Gyselinck (Antwerpen), H. Hainaut (Montegnée), G. Souillet (Lyon), A.-M. Manel (Lyon), G. Margueritte (Montpellier), C. Bachelot (Grenoble).

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For more than 30 years the value of the laboratory researchers who are in charge of the cytology, cytogenetics, immunology and molecular biologic studies has been priceless. Their contributions are and will be of major value for the future of our Group.

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5. Conflict of interest statement

Yves Benoit, Stefan Suciu, Matthias Karrasch, Nicolas Sirvent, Hélène Cavé, Nicole Dastugue, Pierre Rohrlch, Yves Bertrand, Alain Robert, Patrick Lutz, Anne Uyttebroeck, Françoise Mazingue, Alice Ferster, and Lucilia Norton declare no conflicts of interest.

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