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Lessons learnt from the medical and psychosocial evaluation of childhood acute lymphoblastic leukemia (ALL) survivors enrolled in EORTC Children Leukemia Group Trials between 1971 and 1998 and future perspectives for long-term outcome research

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ABSTRACT

Acute lymphoblastic leukemia (ALL) is the most common childhood cancer. With dramatic improvements in survival observed since the 70's, it progressively became evident that the long-term survivors faced late morbidity, late mortality and psychosocial troubles.

In 2010, the EORTC developed the retrospective 58LAE study in order to evaluate the long-term outcome of the 2621 eligible childhood ALL survivors enrolled between 1971 and 1998.

The first sub-project project showed that *ETV6-RUNX1* positive patients had better long-term outcome and had specific sensitivities to treatments. The second sub-project showed that omission of cranial radiotherapy did not increase the risk of relapse and was associated with a higher incidence of second neoplasms and late toxicities in medium and high-risk patients, without central nervous system (CNS) involvement. The third sub-project identified hematopoietic stem cell transplantation, cranial radiotherapy and having a relapse as risk factors for worse socio-economic outcome. Finally, the fertility status of the survivors was also evaluated.

The 58LAE project has raised several challenges when translated into the "real-life" setting, which include the difficulties of following childhood cancer survivors throughout their transition to adult life; the statistical analysis of a cohort of patients treated in multiple clinical trials and along different years; the need for combining different approaches to gather sufficient quality patient data; and the challenge of overcoming the healthcare administrative and regulatory obstacles.

New ways of addressing survivorship studies are needed to address these challenges.

1. The scientific background

Acute lymphoblastic leukemia (ALL) is the most common childhood cancer. The introduction of intensive combinations of chemotherapy, including the use of stem cell transplantation, the refinement of risk-based stratification and the improvement of supportive care resulted in dramatic increase in survival since the 70's. Five-year overall survival progressively raised from 20% in 1970–85% in children (< 14 years) and 62% in adolescents (15–19 years) with contemporary therapy. In parallel, it progressively became evident that the long-term survivors faced late morbidity, late mortality and psychosocial troubles due to ALL and its treatments leading to a shift paradigm from survival to life of quality.

Beside large cohorts of childhood cancer survivors treated with various therapeutic protocols, the European Organization for Research and Treatment of Cancer Children's Leukemia Group (EORTC CLG) initiated a specific long-term outcome evaluation of childhood ALL survivors homogeneously treated in EORTC studies. A long-term update

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of specific randomized questions, taking into account both the long-term survival and the late adverse effects was indeed needed in order to confirm some controversial therapeutic choices, such as the indications of cranial irradiation in childhood ALL. Long-term updates were also warranted in case late relapses were suspected, such as in the *ETV6-RUNX1* positive or hyperdiploid ALL subgroups. Furthermore, late follow-up results are useful to orientate specific therapeutic choices and further adapt the risk-directed therapy in future protocols. Finally, they were necessary to set up specific and standardized long-term follow-up for childhood ALL patients treated in BFM-like studies.

In 2010, the EORTC CLG developed a "Late Adverse Effects" project called "EORTC 58LAE project" (*"Assessment of the long-term outcome of childhood ALL patients enrolled in EORTC Children's Leukemia Group trials between 1971 and 1998"*).

The aims of this retrospective project were to assess the long-term outcome of childhood ALL patients enrolled in EORTC CLG trials between 1971 and 1998:

- Long-term vital status: evaluation of the long-term survival and of the incidence of death due to ALL progression/relapse, acute toxicity, late adverse effects or second malignant neoplasms (SMN).
- Medical data: assessment of the long-term disease status, the incidence and the types of late adverse effects and SMN, and comparison between randomized treatment arms or treatment groups.
- Socioeconomic data: evaluation of the marital status, the education level and work and comparison between randomized treatment arms or treatment groups and with the general population.
- Quality of Life (QOL) data: study of the QOL level of patients of 18 years or older at the time of the 58LAE study enrollment and comparison with the general population, assessment of the impacts of the treatment type, the occurrence of late adverse effects, the occurrence of SMN and/or the socioeconomic status on QOL and health-related QOL (HRQOL).

2. The project

Patients with ALL or lymphoblastic lymphoma who were enrolled as children (less than 18 years old at diagnosis) in EORTC CLG studies between 1971 and 1998 (EORTC studies 58741, 58831/2 and 58881) were eligible in the 58LAE project. For the socioeconomic and QOL evaluations, eligible patients were those eligible in the EORTC study 58LAE and 18 years or older at the time of the evaluation.

Three studies have been conducted between 1971 and 1998 by the EORTC CLG, in order to evaluate the type of consolidation therapy and the type of maintenance therapy (EORTC study 58741), the use of less aggressive regimen for low risk patients (EORTC study 58831), the efficiency of high dose methotrexate to replace cranial radiotherapy for sub-clinical central nervous system (CNS) involvement for medium or high risk patients (EORTC study 58832) and the feasibility of a rapidly rotating and intensive chemotherapy regimen for very high risk patients [1–4] (EORTC study 58881) (see Table 1).

In order to avoid the sending of documents to the family of a deceased patient, the vital status of all patients was first updated (see below, level 1). For identified survivors, an "Information sheet and informed consent form", a "Questionnaire on long-term outcome after leukemia", and QOL questionnaires were sent to the patients by the institutions. Survivors were defined as:

- Alive and agreeing to take part in case they sent back a completed and signed informed consent;
- Alive and disagreeing to take part, by mail or by phone call;
- Lost to follow up in case their contact detail could not be retrieved, or in case the institutions received no answer after two attempts.

For the information that had to be updated (e.g. disease status, late adverse events, SMN or psychosocial data), data retrieval was divided

Table 1
Description of the EORTC studies 58741, 58831/2 and 58881.

EORTC study number	Eligible patients	Sample size	Study open k closed	Involved countries	Aim of the study
58741	ALL < 50 years	224 < 50 years 195 < 18 years	1971–1978	Belgium	Type of consolidation therapy (3 versus 7 drugs) Type of maintenance therapy (chemotherapy versus immunotherapy)
58831/2	ALL < 18 years	788	1983–1989	Belgium France	Evaluation of less aggressive regimen without cyclophosphamide (58831 study) Evaluation of cranial radiotherapy (CRT) when given after high-dose methotrexate (HD MTX) and evaluation of the efficiency of HD MTX to replace CRT for sub-clinical central nervous system involvement in high risk patients (58832 study)
58881	ALL/non-Hodgkin lymphoma < 18 years	2216	1989–1998	Belgium France Portugal	Evaluation of cytarabine during interval therapy in association with HD MTX for medium risk patients Evaluation of monthly intravenous 6-mercaptopurine during maintenance for low risk and medium risk patients Predictive significance of minimal residual disease at completion of induction Comparison of E. Coli and Erwinia L-Asparaginase Feasibility of a rapidly rotating and intensive chemotherapy regimen for very high risk patient