Belgian Society of Paediatric Haematology Oncology symposium

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Epidemiological data: cancer in children and adolescents in Belgium

L. Van Eycken - Cancer Registry, Belgium

Each year 2.65 million individuals are diagnosed with cancer in Europe. In 2011, more than 64,000 patients were newly diagnosed with cancer in Belgium; 320 of them were children younger than fifteen years of age and 175 were adolescents between fifteen and nineteen years old. Therefore, childhood and adolescent cancer is rare, i.e. less than 1% of all cancers. The incidence is two to three times higher in infants than in children between three and ten years, and increases again after the age of ten years. At all ages, boys are more frequently affected than girls (1.2:1 ratio).

The most frequent type of cancer in children is leukaemia (25%), while lymphoma constitutes 12% of cancers in children. In adolescents, lymphoma is more frequent (25%) than leukaemia (12%).

The cancer registry obtains information on new diagnoses from different sources: paediatric haemato-oncology centres, multidisciplinary oncology consult (MOC), health insurances, pathology laboratories, and/or clinical biology. Data were used to analyse incidence and survival and results for leukaemia and lymphoma between 2004 and 2010 have been presented.

Overall, acute lymphoblastic leukaemia (ALL) is more frequent than acute myeloid leukaemia (AML) in patients younger than nineteen years of age: 74% versus 17%, but the relative frequency varies by age: in infants AML occurs as frequently as ALL, while in children between one and four years old AML is much less frequent than ALL. In adolescents, AML is almost as frequent as ALL. The observed five-year survival of ALL is 87%, while the five-year survival of AML is 63%. The survival for B-cell ALL is slightly better than for T-cell ALL, which is in contrast with data in adults. Moreover, infants with ALL have the worst prognosis, whereas survival is the best (> 90%) for children between one and four years old. In contrast, there is not much difference in survival rates for AML between age groups.

Observed five-year survival rate of adolescents with Hodgkin's lymphoma is around 97%, and that for non-Hodgkin's lymphoma is 87%.

The yearly incidence of childhood leukaemia in Europe increases by 1% per year (0-14 years), but numbers in Belgium are too small to draw any conclusions from this. For lymphoma, the yearly incidence remained stable over the years. Fortunately, the mortality rate has decreased by 3% per year.

Late effects of childhood cancer treatments

C. Piette - University of Liège, Belgium

Advances in cancer therapy during the past 40 years have resulted in a remarkable increase in survival of childhood and adolescent cancer. About one out of 640 adults between 20 and 39 years of age have survived cancer during their childhood. As a result, about 4,300 adults of that age in Belgium are survivors of childhood cancer. Yet, a growing number of people are at risk for

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long-term complications, including late mortality, secondary malignancies, late toxicity and quality of life issues.

Late mortality

A large retrospective analysis of more than 20,000 individuals who survived more than five years after the diagnosis of childhood cancer between January 1970 and December 1986 (Childhood Cancer Survivor Study) reported an absolute excess of seven deaths per 1,000 individuals followed for one year. This increased mortality continues to be present even 30 years after diagnosis. The development of second malignancies is one of the most devastating complications of cancer therapy. Other complications include cardiotoxicity, growth retardation, obesity, endocrine disorders, fertility impairment and central nervous system (CNS) disorders. The main cause of death within the first fifteen years of follow-up is recurrence of the tumour, while secondary malignancies and cardiotoxicity gain importance after 20 to 25 years of follow-up. However, the risk depends on the type of the primary diagnosis, gender (higher in females), age (higher if diagnosed at younger age), and on the initial treatment (e.g. cardiotoxicity after anthracyclines or cardiac radiotherapy; second cancers after radiotherapy or alkylating agents).

Secondary malignancies

The cumulative incidence of secondary malignancies after childhood cancer continues to increase without plateau and reaches 5% at 25 years of follow-up. The most common secondary tumours are bone tumours, breast cancer and thyroid cancer. Several risk factors influence the incidence of secondary malignancies. Girls and children who are younger at diagnosis are at increased risk for a secondary malignancy. In addition, some types of cancer (e.g. Hodgkin's lymphoma and soft tissue sarcoma) and treatment modalities (e.g. radiotherapy and alkylating agents) are associated with an increased risk. A genetic predisposition may also play a role.

Late toxicity

Many adults who survived childhood cancer experience long-term toxicity. Thirty years after diagnosis, 70% of patients have at least one chronic condition, which is severe or life-threatening in 40%. The incidence and severity of these chronic conditions tend to increase over the years. The cause of late toxicity is multifactorial (type of tumour, gender, age at diagnosis, comorbidity, etc.) but the initial treatment has the most important impact. Guidelines for long-term follow-up are available online (Children's Oncology Group: http://www.survivorshipguidelines.org/).

Quality of life issues

Apart from physical sequelae, childhood cancer and its treatment also have an impact on the social life (e.g. marriage) and psychological outcome (e.g. depressive symptoms and antisocial behaviour). Those survivors may also experience problems at school and/or work due to difficulties linked to neurocognitive deficits. More than 10% of survivors of childhood cancer suffer from post-traumatic stress syndrome.

Long-term follow-up

Large studies have given us better insight into the long-term complications of cancer and its treatment during childhood or adolescence. However, many questions regarding good long-term follow-up remain.

Multidisciplinary collaboration between the paediatric haemato-oncologist, general practitioner, adult internist and patients themselves is essential for a good follow-up. Each medical doctor has partial knowledge needed for such a follow-up. The general practitioner should integrate recommendations for follow-up, made by the paediatric haemato-oncologist and based on the individual calculated risk, depending on the type of cancer and treatment given. Frequency of follow-up should be standardised, based on the calculated risks but avoiding unnecessary examinations. In addition, the approach should be global, including psychologists and social workers, as well as prevention provided by a dietician and tobaccologist.

Anaplastic Large Cell Lymphoma in children and adults: state of the art

L. Brugières - Institut Gustave Roussy, Villejuif, France

Anaplastic Large Cell Lymphoma (ALCL) is a rare type of lymphoma in adults and in children but among mature T-cells lymphomas, ALCL is more common in children than in adults and constitutes about 10-15% of all childhood lymphomas, i.e. > 80 cases per year in Europe. Most cases of ALCL in childhood (> 90%) are ALK (anaplastic lymphoma kinase) positive, which is in contrast to ALCL in adults. ALK-positive ALCL shows a broad spectrum of morphological features with five morphological patterns now recognised by the World Health Organisation (WHO).

Three factors were associated with a high risk of relapse: presence of skin lesions, mediastinal and visceral involvement. Atypical histological subtypes (small cell or lymphohistiocytic components) also indicate higher risk of relapse. More recently, new biological risk factors have been published: patients with a negative PCR for ALK transcripts in the bone marrow or blood and a

high anti-ALK titer had a better prognosis. These results should be used to stratify patients in future ALCL trials to optimise treatment.

Standard therapy nowadays consists of multidrug first-line chemotherapy but very different regimens are used concerning duration of treatment, number and cumulative doses of drugs. All result in similar event-free survival (EFS) rates of about 65-75%. Addition of weekly vinblastine during twelve months did not improve outcomes, but prolonged duration of methotrexate infusion (24 hours versus 3 hours) caused more toxicity (ALCL99 trial). However, the duration of vinblastine may have been too short in this trial.

In relapsed or refractory ALCL, vinblastine monotherapy has been shown to be highly efficient and to produce durable remissions (five-year EFS 30%; five-year overall survival (OS) 65%). The role of the immune system in controlling ALCL might partly explain the efficacy of vinblastine as this cytostaticum has been shown to be a potent inducer of dendritic cell maturation.

Options for bad prognostic patients include the administration of Brentuximab Vedotin or Crizotinib. A response rate of 86% and twelve-month survival rate of 70% was obtained with Brentuximab Vedotin at a dosage of 1.8 mg/kg/3 weeks. Studies reported 87.5% complete remission rate obtained in children treated with Crizotinib (280 mg/m^2 BID). Promising results for Crizotinib were also found in adults.

Future studies are needed to evaluate the best therapeutic option for intermediate and high risk patients: vinblastine as first line therapy versus new drugs at front.

T-cell non-Hodgkin's lymphoma in children and adolescents

A. Uyttebroeck - University Hospitals Leuven, Belgium

Results of EORTC studies for T-cell non-Hodgkin's lymphoma (NHL) in children and adolescents were presented. Lymphoblasts in T-cell NHL and T-cell ALL share the same features. In the Berlin-Frankfurt-Munster (BFM) trials, patients with T-cell NHL are therefore treated according to an ALL strategy. A BFM-like EORTC protocol (EORTC 58881) without prophylactic CNS radiotherapy demonstrated an EFS at six years of 77.5% and an OS of 85.7%, which is comparable with prior studies including cranial irradiation. Relapses occurred in 16% at a median time of one year. The CNS recurrence rate was low (2%). A follow-up EORTC study (EORTC 58951) demonstrated increased EFS of 85.1% with a similar OS of 86.5%, due to intensified therapy during induction for patients with stage III and IV lymphoma. Yet, the chance of survival in case of relapse is poor. Randomisation for prednisolone during induction clearly improved outcome but a higher mortality rate in complete remission hampered the outcome in children receiving dexamethasone. A good non-haematological response to the prephase therapy has been identified as a good prognostic factor and there is a trend towards significance for females older than nine years having a poorer prognosis. Also loss of heterozygosity on chromosome 6q14-q24 has been associated with poor outcome in paediatric T-cell NHL.

Future studies are needed to better identify risk factors and genetic markers, to reduce toxicity and to propose new therapeutic options for relapsed patients.

T-cell acute lymphoblastic leukaemia in children and adolescents

B. De Moerloose – University Hospital Ghent, Belgium

Results of the same EORTC studies were also presented for T-cell ALL. In contrast with NHL, the lymphoblastic count in the bone marrow of ALL patients amounts to more than 25% and/or peripheral blasts are present. T-cell ALL constitutes less than 15% of all childhood ALL cases.

Males are predominantly affected, with a mean age of ten years. A mediastinal mass is commonly present (61%) and CNS involvement is more frequent (9%) than in T-cell NHL. Comparing the results of the EORTC 58951 and the EORTC 58881 trial, an improved eight-year EFS was reported (74% versus 65.1%) thanks to optimisation of systemic and CNS-directed therapy. Besides, these results are comparable with previously published data on EFS, indicating that omitting cranial irradiation does not worsen prognosis. Other studies have also confirmed that protocols with or without cranial radiotherapy have similar EFS rates. Yet, the optimal number of intrathecal chemotherapeutic injections remains unknown.

In addition, randomisation between Escherichia coli (E. coli) asparaginase and Erwinia asparaginase (EORTC 58881) or between prednisolone and dexamethasone (EORTC 58951) demonstrated an improved EFS and OS with E. coli asparaginase and prednisolone. Best outcome was seen in patients with a white blood cell count less than 100 x 10^9/μl at diagnosis and good response to prephase therapy (eight-year EFS 84.6%; eight-year OS 93%).

Finally, future progress in understanding genetic mechanisms will improve the classification in prognostic subsets as well as allow targeted therapies.

Molecular insights in acute lymphoblastic leukaemia

K. De Keersmaecker - Centre for Human Genetics, Catholic University Leuven, Belgium

T-cell ALL arises from the malignant transformation of haematopoietic progenitor cells primed toward T-cell development, as the result of a multistep oncogenic process involving constitutive activation of NOTCH signalling and genetic alterations in transcription factors, signalling oncogenes, and tumour suppressor genes.

The NOTCH1 heterodimer contains an extracellular and transmembrane subunit. Upon physiologic activation of the NOTCH receptor a cascade of cleavages in the transmembrane subunit is initiated, generating intracellular NOTCH, which translocates to the nucleus and forms a large transcriptional activation complex. Mutations have been reported to result in activation in the absence of ligand binding to the NOTCH receptor or in stabilisation of intracellular NOTCH and are highly prevalent in T-ALL. This has prompted investigation of therapeutic targeting of this signalling pathway, which is now in clinical testing for the treatment of T-ALL. The concomitant use of dexamethasone helps to overcome the gastrointestinal toxicity associated with systemic inhibition of the NOTCH pathway.

Transcription factors are also well-known to be deregulated by chromosomal translocations in T-ALL: e.g. overexpression of TLX causing poor rearrangement of T-cell receptor alpha and thus inducing a maturation arrest in the developing T-cell. In contrast, mutations in protein tyrosine kinases have been identified only rarely (e.g. NUP214-ABL1 transcript) and these patients may also be candidates for targeted therapy.

More recently, new players in the development of T-ALL have been identified by next generation sequencing: X-linked plant homeodomain finger six gene mutations (16% of paediatric T-ALLs and 38% of adult T-ALLs); mutations in EZH2 and SUZ12 genes (25% of T-ALLs), which encode crucial components of the Polycomb repressive complex 2 (PRC2) resulting in impaired chromatin compaction. Interestingly, it has been found that NOTCH antagonises the activity of this PRC2. In addition, exome sequencing identified mutations affecting the ribosomal proteins RPL5 and RPL10 in 9.8% paediatric T-ALLs and identified CNOT3 mutations in 7.9% of adult T-ALLs (0.8% of children). Although the function needs to be investigated further, CNOT3 seems to be involved in degradation of RNA and self-renewal of cells.

Molecular insights in acute myeloid leukaemia

M. M. van den Heuvel-Eibrink - University Medical Centre Rotterdam, the Netherlands

AML constitutes 15-20% of all paediatric leukaemias. Despite intensive chemotherapy, overall cure rates of AML in most contemporary treatment protocols remain around 70%. Further improvements in survival are not likely to come from even more intensive therapy as treatment-related mortality is already important, but targeted therapy based on a better understanding of molecular abnormalities responsible for the formation and growth of leukaemic cells will provide new therapies. AML is a very heterogeneous disease with several cytogenetic subgroups. Class I mutations (e.g. Flt3-internal tandem duplication) result in proliferation advantage whereas class II mutations (e.g. MLL-rearrangement) inhibit differentiation. These various genetic subtypes are linked with marked differences in cure rates. For example, a collaborative study on 756 MLL-rearranged patients has identified t(9;11) as a group with intermediate outcome; in particular patients with FAB M5 type AML and a white blood cell count below 50 x $10^9/\mu l$ at diagnosis seem to have a better prognosis. Other translocation partners of chromosome 11 resulting in MLL-rearrangement are associated with poor outcome with the exception of t(1;11) indicating a very good prognosis. Besides, about one quarter of paediatric AML patients are classified as 'cytogenetically normal', compared to 45% of adults with AML. Recently, molecular aberrations with prognostic significance have also been identified in these adults. Mutations in the WT1 gene (present in 11.7% of paediatric AML) result in overexpression of the WT1 transcription factor and are associated with a very poor prognosis while mutations in the NMP1 gene (8.6% of paediatric AML versus 50-60% of adult AML) have a favourable prognosis even in the presence of Flt3 mutation. Genome-wide techniques have further identified novel genetic aberrations: translocations causing NUP98/NSD1 fusion and NUP98/JARID1A have been described in 16% of paediatric 'cytogenetically normal' AML patients and are associated with poor prognosis. NUP98 belongs to a multiprotein structure responsible for traffic between the nucleus and the cytoplasm and fusion proteins activate transcription of the homeobox (HOX) genes. Those HOX genes are transcription factors playing a role in the development of the haematopoietic system: expression promotes stem-cell self-renewal. To date, around 15% of 'cytogenetically normal' AMLs have not yet been unravelled. Epigenetics might play a role in those patients.