

Acute Leukemia in Children

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Abstract: Acute leukemia is the most common childhood cancer and accounts for 31% of all cancers in children. There are two main types of acute leukemia. The most common is ALL (acute lymphoblastic leukemia) affecting the lymphoid lineage, and the more rare AML (acute myeloid leukemia) affecting the myeloid lineage. The intention of this thesis is to follow the course of treatment from the admission to the hospital until the last check up and also see how a child will react to the treatment and side effects in later life. We studied literature and my own case records from the period when I was treated for ALL. From the literature and my case records, we can see that children tolerate treatment quite well. Due to rapid diagnostics and the possibility to give high doses chemotherapy, the overall prognosis appears to be very good. Today, acute leukemias of paediatric patients have a really favourable prognosis. The overall survival rate for ALL is higher than 80% and for AML 65%. So the results are good, but there is still a long way to go before we can be satisfied. To date we do not have a contingency program for children treated for acute leukemia after 18 years of age (neither in Norway or Slovakia) so perhaps this should be a focus point in the future. It could be extended to follow up patients in adulthood in order to monitor late effects that may occur in later life after many years of treatment.

Key words: Acute leukemia, ALL, AML.

Abbreviations

ACTH	Adrenocorticotrophic hormone
ALAT	Alanine aminotransferase
ALL	Acute lymphoblastic leukemia
AML	Acute myeloid leukemia
ASAT	Aspartate aminotransferase
BBB	Blood brain barrier
BM	Bone marrow
BNP	Brain type natriuretic peptide
CMV	Cytomegalovirus
CNS	Central nervous system
CRP	C-reactive protein
CT	Computertomography
CVC	Central vein catheter
FAB	French American British
FCA	Flow cytometric analysis
FISH	Fluorescence in situ hybridisation
Gamma GT	Gamma glutamyl transpeptidase
GIT	Gastrointestinal tract
GP	General practitioner
GFR	Glomerular filtration rate
GVHD	Graft versus host disease
Hb	Hemoglobin
Hct	Hematocrit
HE	Haematoxylin and eosin stain

HR	High risk group
HSV	Herpes simplex virus
IgA	Immunoglobulin A
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IR	Intermediate risk group
LD	Lactate dehydrogenase
MRD	Minimal residual disease
MTX	Methotrexate
PCR	Polymerase chain reaction
PTSD	post traumatic stress disorder
RBC	Red blood cell count
SR	Standard Risk group
TBC	Thrombocytes
VZV	Varicella zoster virus
WBC	White blood cell
WHO	World Health Organization
NOPHO	Nordic Society of Paediatric Hematology and Oncology

1. Introduction

1.1 History

Acute leukemia, the most common form of paediatric cancer has become one of the success stories in the field of oncology. This once fatal disease is now curable in the majority of paediatric patients who

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receive fast and appropriate treatment [1, 2]. In the 1970 era, approximately 10% of all children diagnosed with any type of paediatric cancer survived. Since then, there has been a tremendous development, and today 80% survive [3].

1.2 Definition

Acute leukemia is a malignant clonal disorder in one or more cell-lines in the hematopoietic system. It is the most common form of childhood leukemia, and comprises 1/3 of all paediatric cancers (Fig. 1). There are two main types of acute leukemia found in children. The most common is ALL (acute lymphoblastic leukemia) (Fig. 2), and the more rare AML (acute myeloid leukemia). In Norway, there are 30~40 cases per year in children from 0~14 years [1, 4].

ALL is a malignant clonal disorder that affects the lymphoid line in the hematopoietic blood system. It is a high count of immature lymphocytes, called lymphoblasts. The diagnosis can be confirmed when there are more than 25% lymphoblasts in the bone marrow picture.

The cancer cells can arrive either from B or T cells, where immature precursors of B are most common (90%). In Norway and Slovakia, they follow NOPHO

treatment protocol and differentiate ALL into three groups: standard risk, intermediate risk and high risk. Allocating each child to a risk group is dependent on cell type, leukocyte count, cytogenetics and how he/she responds to the given treatment [1, 4].

AML is a malignant clonal disorder of myeloid cells. It is a heterogeneous, clonal disturbance in the hematopoietic cells. They lose their capability to differentiate normally and to respond to normal regulatory mechanisms in proliferation. According to FAB classification, there must be a presence of at least 30% blasts in the BM. WHO classification has lowered the criteria to at least 20%. AML accounts for approximately 15 % of leukemias in children, and is rare. It can affect all age groups, and is more common in adults. Paediatric AML is more difficult to treat than ALL. And in comparison to ALL where it is more common to use WHO classification, we use FAB classification in AML. We have eight groups M0-M7. M3, also called “acute promyelocytic leukemia”, has a special translocation t(15; 17). This type of leukemia is treated with a special protocol. Also M7 called “megakaryocytic leukemia” is extremely rare and very difficult to treat [1, 4, 5].

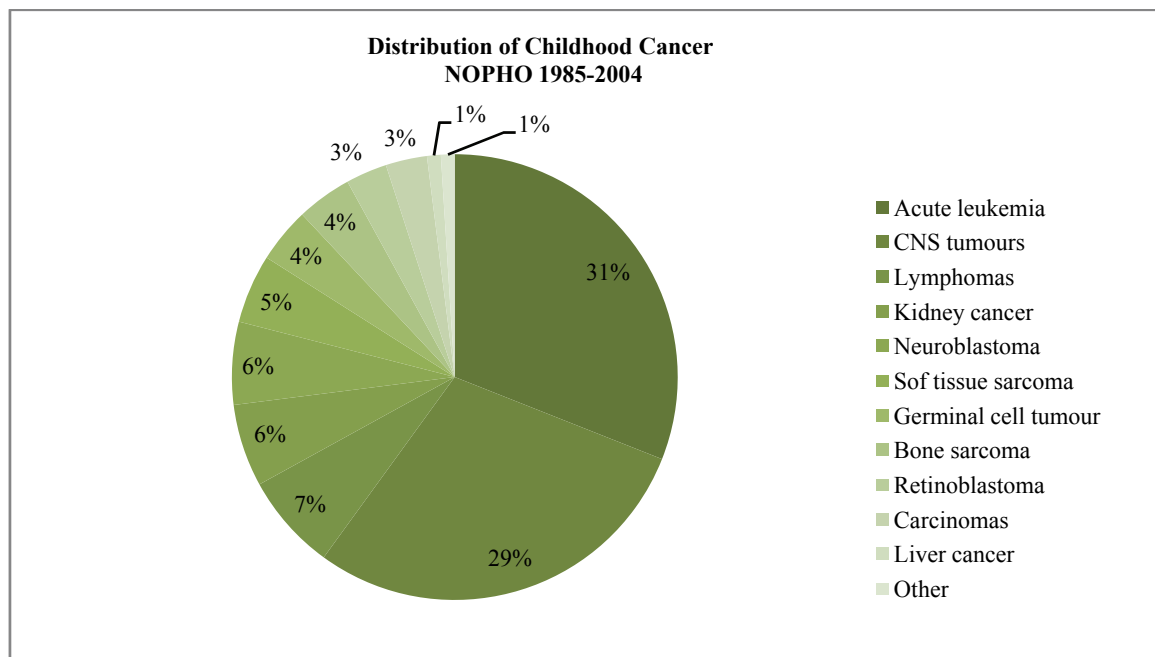


Fig. 1 Distribution of paediatric cancer [1].

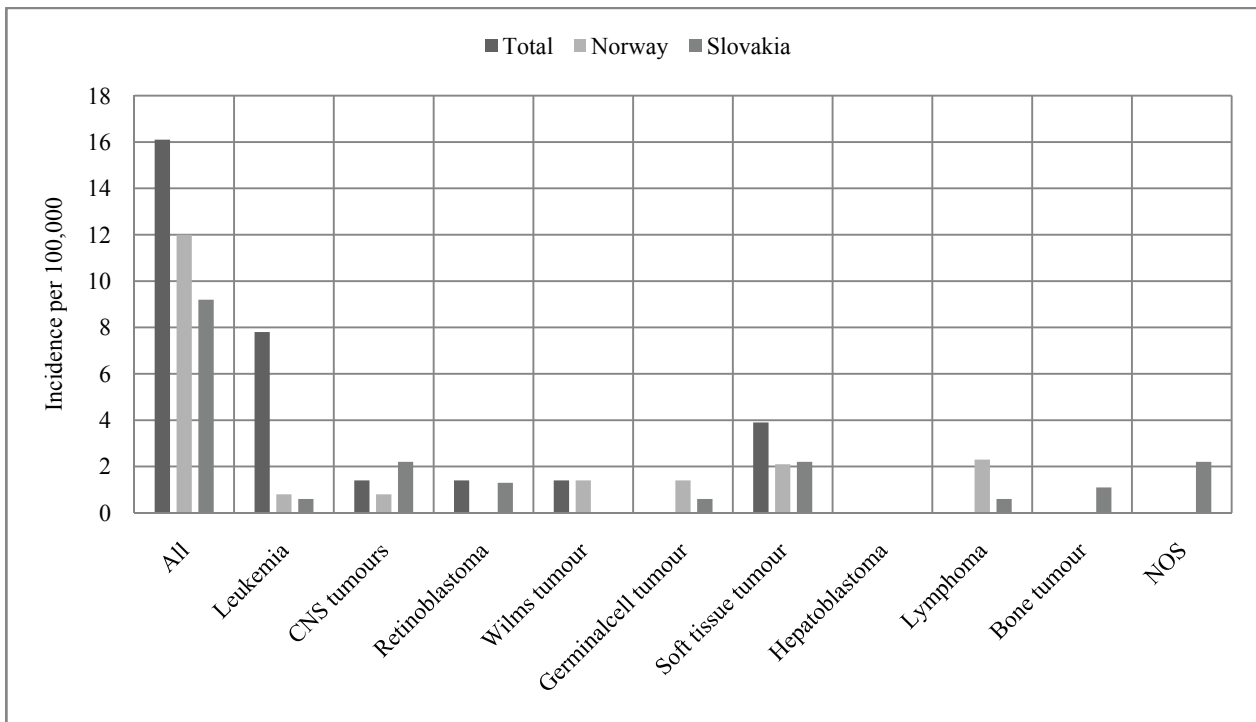


Fig. 2 Age specific incidence according to Norway and Slovakia.

2. Theoretical Part

2.1 Classification

Classification is the language of medicine: Diseases must be described, defined and named before they can be diagnosed, treated and studied, from WHO.

There are two classifications used in the definition of acute leukemias: FAB (French American British classification) and WHO (World Health Organisation). The difference between the two classifications is mostly related to the number of blasts in the BM. According the FAB criteria, number of blasts in the bone marrow should be more than 30%. WHO has a criterion of 20%. FAB classification is mostly based on morphology and cytochemistry. WHO on the other hand is based on clinical, cytogenetic and molecular abnormalities. WHO is the newest classification, and is widely used for leukemia, especially ALL.

2.2 WHO Classification

In 2007, WHO updated their classification of tumours of haematopoietic and lymphoid tissues [6].

This is a widely-used classification which can be found on many publications, such as the articles from Vardiman et al. [7] and Mautes et al. [8].

- AML and related precursor neoplasms;
- AML with recurrent genetic abnormalities:
 - (1) AML with t(8; 21) (q22; q22); RUNX1-RUNX1T1;
 - (2) AML with inv (16) (p13.1; q22); CBFB-MYH11;
 - (3) Acute promyelocytic leukemia with t(15; 17) (q22; q12); PML-RARA;
 - (4) AML with t(9; 11) (p22; q23); MLLT3-MLL;
 - (5) AML with t(6; 9) (p23; q34); DEK-NUP214;
 - (6) AML with inv (3) (q21; q26.2) or t(3; 3) (q21; q26.2); RPN1-EVI1;
 - (7) AML (megakaryoblastic) with t(1; 22) (p13; q13); RBM15-MKL1;
 - (8) AML with mutated NPM1;
 - (9) AML with mutated CEBPA;
- AML with myelodysplasia-related changes;
- Therapy related myeloid neoplasms;
- Acute myeloid leukemia, NOS:
 - (1) AML with minimal differentiation;

- (2) AML without maturation;
- (3) Acute myelomonocytic leukemia;
- (4) Acute monoblastic and monocytic leukemia;
- (5) Acute erythroid leukemia;
- (6) Acute megakaryoblastic leukemia;
- (7) Acute basophilic leukemia;
- (8) Acute panmyelosis with myelofibrosis;
- Myeloid sarcoma;
- Myeloid proliferations related to down syndrome:
 - (1) Transient abnormal myelopoiesis;
 - (2) Myeloid leukemia associated with Down syndrome;
 - Blastic plasmacytoid dendritic cell neoplasm;
 - Acute leukemias of ambiguous lineage:
 - (1) Acute undifferentiated leukemia;
 - (2) Mixed phenotype acute leukemia with t(9; 22) (q34; q11.2); BCR-ABL1;
 - (3) Mixed phenotype acute leukemia with t(v11q23); MLL rearranged;
 - (4) Mixed phenotype acute leukemia, B/myeloid, NOS;
 - (5) Mixed phenotype acute leukemia, T/myeloid, NOS;
 - Precursor lymphoid neoplasms;
 - B lymphoblastic leukemia/lymphoma:
 - (1) B lymphoblastic leukemia/lymphoma, NOS;
 - (2) B lymphoblastic leukemia/lymphoma with recurrent genetic abnormalities;
 - (3) B lymphoblastic leukemia/lymphoma with t(9; 22) (q34; q11.2); BCR-ABL1;
 - (4) B lymphoblastic leukemia/lymphoma with t(v11q23); MLL rearranged;
 - (5) B lymphoblastic leukemia/lymphoma with t(12; 21) (p13; q22); TEL-AML1 (ETV6- RUNX1);
 - (6) B lymphoblastic leukemia/lymphoma with hyperdiploidy;
 - (7) B lymphoblastic leukemia/lymphoma with hypodiploidy (hypodiploid A);
 - (8) B lymphoblastic leukemia/lymphoma with t(5; 14) (q31; q32); IL3-IGH;
 - (9) B lymphoblastic leukemia/lymphoma with t(1;

19) (q23; p13.3); E2A-PBX1 (TCF3- PBX1).

2.3 FAB Classification

French American British classification is a much older classification, but still widely used today [9]. It is a much easier classification and mostly used in the diagnosis of AML.

FAB classification divide AML into eight subtypes M0-M7:

- M0—Minimally differentiated AML;
- M1—AML without maturation;
- M2—AML with maturation;
- M3—Acute promyelocytic leukemia;
- M4—Acute myelomonocytic leukemia;
- M5—Acute monocytic leukemia;
- M6—Acute erythroleukemia;
- M7—Acute megakaryocytic leukemia.

FAB classification divide ALL into three subtypes:

- L1—Childhood-ALL (B-ALL, and T-ALL);
- L2—Adult ALL (mostly T-ALL);
- L3—Burkitt type ALL (B-ALL).

2.4 Feature AML and ALL

Both AML and ALL have many of the same clinical features, and it is not possible to distinguish them only on clinical signs [10]. The importance of morphology, cytogenetic and immunophenotyping is invaluable when talking about diagnosis of acute leukemia. Table 1 shows the most contrasting features of AML and ALL (taken directly from Ref. [10]).

2.5 Etiology

There is no exact etiology which positively defines leukemia. To date, it would seem that acute leukemia is not related to any specific group of children and their respective circumstances and why they get the disease but some studies show that certain risk factors can precipitate it. The early detection and treatment is therefore more difficult. Twins have a higher frequency of occurrence if one of them develops leukemia. High doses of radiation in utero, so limiting the use of

Table 1 Overview of the contrasting feature of AML and ALL [10].

Feature	AML	ALL
Common age	Adults between 15~40 years; Comprise 20% of childhood leukemia Children < 15 years	Comprise 80% of childhood leukemias
Physical findings	Splenomegaly + Hepatomegaly + Lymphadenopathy + Bony tenderness + Gum hypertrophy +	Splenomegaly ++ Hepatomegaly ++ Lymphadenopathy ++ Bony tenderness ++ CNS involvement ++
Laboratory findings	Low to high TLC; predominance of myeloblasts and promyelocytes in blood and bone marrow; Thrombocytopenia moderate to severe	Low-to-high TLC, predominance of lymphoblasts in blood and bone marrow; Thrombocytopenia moderate to severe
Diagnostic criteria	FAB types M0-M7 WHO criteria $\geq 20\%$ blasts	FAB types L1-L3, WHO types Pre B (90%) Pre T (10%) WHO criteria $\geq 20\%$ blasts
Cytochemical stains	Myeloperoxidase +, Sudan black +, NSE + in M4 and M5, acid phosphatase (diffuse) + in M4 and M5	PAS +, acid phosphatase (focal) +
Specific therapy	Cytosine arabinoside, anthracyclines (daunorubicin, adriamycin) and 6-thioguanine	Vincristine, prednisolone, anthracyclines and L-asparaginase
Immunophenotyping	CD13, 33, 41, 42	Both B and T cell AL Tdt +ve Pre B: CD19,20 Pre T: CD1,2,3,5,7
Cytogenetics	M3: t(15; 17) M4: in (16)	Pre B: t(9; 21)
Response to therapy	Remission rate low, duration of remission shorter	Remission rate high, duration of remission prolonged
Median survival	12~18 months	Children without CNS prophylaxis 33 months, with CNS prophylaxis 60 months; Adults 12~18 months

diagnostic (CT) and therapeutic radiation are important initiatives. Some hereditary diseases or syndromes are more prone: Down's syndrome, Fanconi's anemia and ataxia telangiectasia has a slighter increased risk for developing acute leukemia [1, 4, 11].

2.6 Symptoms

Symptoms of leukemia in children can vary greatly, and most of them are unspecific but can be a result of reduced bone marrow function. Other symptoms include bleeding, often present as petechiae is a feature of thrombocytopenia: Fever and infections (caused by low white blood cell count), some features of anemia such as fatigue, paleness and dyspnea. The child can also experience pain due to expansion of the bone marrow, often related to a joint or skeleton. The immature blasts can infiltrate other tissue and the patient will have symptoms like swollen lymph nodes, hepatomegaly, splenomegaly, swelling of testicles and kidney infiltration. If the CNS is involved, the child can complain about headache, double vision and pathological changes in cranial nerves. Usually the symptoms are vague, and the child can experience

several infections before the diagnosis is confirmed [1, 4, 12, 13].

2.7 Risk Groups

Acute leukemia is divided into risk groups instead of stages as most other cancer types in adults.

According to NOPHO protocol, ALL is differentiated into three risk groups, based on cell type, leukocyte count at diagnosis, cytogenic criteria and treatment response:

(1) Standard risk:

- Age 1~17.9 years;
- Leukocytes at diagnosis < 100;
- Pre-B ALL;
- No high-risk cytogenetic criteria;
- Positive response to therapy;
- MRD (minimal residual disease) < 10⁻³ on Day 29 and Day 79 of therap;

(2) Intermediate risk:

- Age 1-17.9 years;
- Leukocytes at diagnosis < 100;
- Pre-B ALL;
- CNS involvement (CNS3) at diagnosis;

- Following cytogenetic changes: t(1; 19) ic21amp dic 9; 20;

- No MRD marker available; or MRD > 10-3 Day 29 and < 10-3 Day 79;

High risk group at the start (leukocytes > 100 and/or T cell ALL) and no high risk cytogenetic changes (11q23 aberrations, hypodiploidy), but good response, MRD < 10-3 day 29 and day 79.

(3) High risk:

- Age 1-17.9 years;

- Leukocytes at diagnosis > 100 and/or T-ALL and MRD < 10-3 day 29. Or leukocytes at diagnosis < 100 and pre-B ALL, but high risk cytogenetic changes (hypodiploidy, 11q23 aberrations);

- A poor treatment response, either MRD Day 29 > 5 [4].

In addition, there are two special groups: infant leukemia and Philadelphia chromosome positive ALL. Both groups have their own protocol [4].

AML is not divided into risk groups the same way as ALL. It is divided into two risk groups based on the treatment response. Poor treatment response leads to upgrading to a higher risk group [4].

2.8 Differential Diagnosis

During the investigation of a child with suspected acute leukemia, it is important to consider other diagnosis as well. The differential diagnosis can be aplastic anemia, ITP (idiopathic thrombocytopenic purpura), acute anemia, Hemolytic uremic syndrome, infections with bone marrow suppression (CMV, EBV, parvovirus B19, HHV-6), rheumatoid arthritis, TMD (transient erythroblastopenia, myeloproliferative disease), DIC (disseminated intravascular coagulation) [6, 14].

2.9 Prognosis

With improved diagnostic, chemotherapy, hematopoietic stem cell transplantation and supportive care, the prognosis of paediatric acute leukemia has improved considerably during the past decades. The

overall survival rate for ALL is > 80% and for AML 65%. This development has been a fantastic success as 50 years ago success like this was simply the stuff of dreams. Today, the focus has changed somewhat and paediatric protocols have produced great results as research has shown that, by adapting treatment and using therapy that neither over treats nor under treats the patient, results are very much improved [15].

Even though we often refer to paediatric cancer as a success story, some still do not survive. According to the paediatric cancer society in Norway (barnekreftforeningen.no) 4/5 kids survive. So 20% of all paediatric patients treated for any type of cancer will die.

2.10 Diagnosis

Diagnosis is based on a combination of morphology, immunophenotyping, cytogenetic and other clinical features. AML and ALL have many of the same clinical features, and it is difficult to distinguish between them based solely on clinical manifestations.

2.10.1 ALL

Patients with ALL will also have symptoms of BM failure: thrombocytopenia, anaemia and neutropenia (Figs. 3 and 4). The leucocyte count can vary from leucopenia to leucocytosis. The differential leucocyte count will show an increased number of lymphoblasts. Other signs can be lymphadenopathy, hepatomegaly, splenomegaly, CNS infiltration, testicular enlargement and infections.

The morphology of the bone marrow will show lymphoblasts of either B or T cell lineage, reduced amount of red blood cells, and either absent or reduced number of megakaryocytes. The lymphoblasts in B-ALL often have scant cytoplasm and condensed nuclear chromatin. Periodic acid-Schiff, Acid phosphatase, Myeloperoxidase, Sudan Black and Non-specific esterase are used in characterisation of leukemic blasts.

The immunophenotyping is a fantastic method to

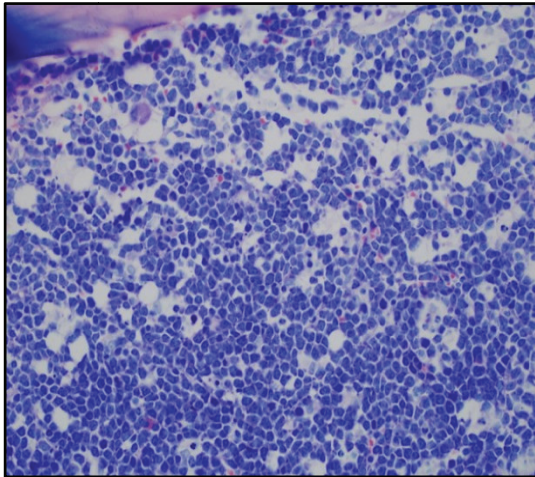


Fig. 3 BM, ALL, Giemsa stain and predominantly lymphoblasts. Photos from the register of Prof. Plank, Department of Pathology in Martin, Slovakia. Accessed April 2015.

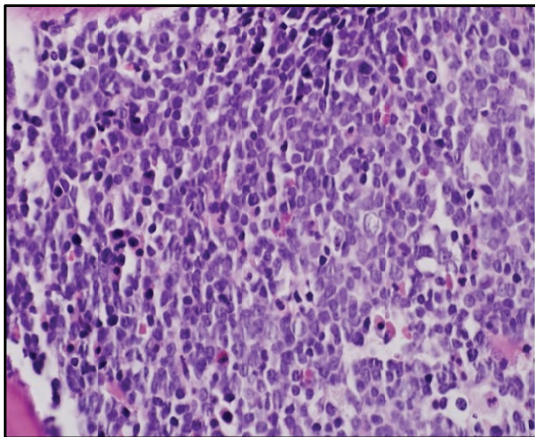


Fig. 4 BM, ALL, HE stain, predominantly lymphoblasts. Photos from the register of Prof. Plank, Department of Pathology in Martin, Slovakia. Accessed April 2015.

distinguish lymphoid from myeloid origin and vice versa. It will show which antigen and enzymes that are expressed on the cells. Tdt will always be present in pre-B and pre-T cell acute lymphoblastic leukemia. For B cell type, other markers typically present is CD19, CD10 and CD79a (Figs. 5 and 6). For T cell type it is commonly CD1, CD2, CD3, CD5 and CD7.

Cytogenetic abnormalities like translocations can have specific prognostic features. For example, pre-B ALL can show cytogenetic abnormality of t(9; 22), i.e., Philadelphia positive ALL. Leukemia with specific translocations often has specific protocols with individualized treatment.

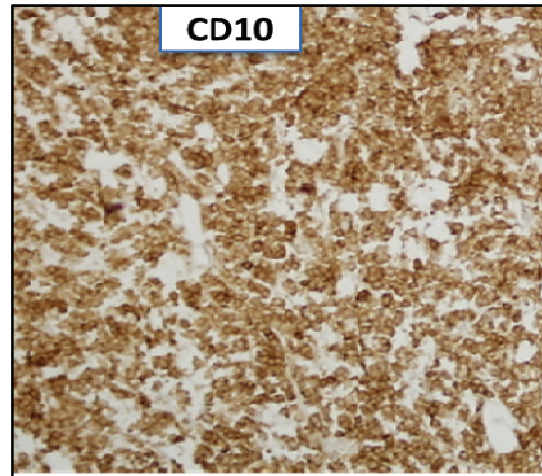


Fig. 5 CD10. Photos from the register of Prof. Plank, Department of Pathology in Martin, Slovakia. Accessed April 2015.

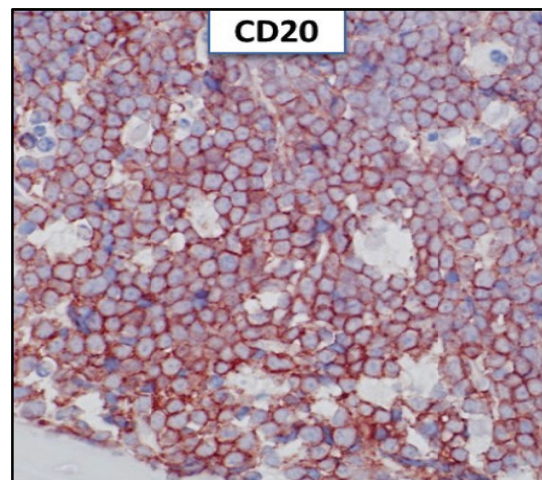


Fig. 6 CD20. Photos from the register of Prof. Plank, Department of Pathology in Martin, Slovakia. Accessed April 2015.

This is primarily a disease affecting children and 75% of the children are under six years of age. Approximately 85% of ALL is a pre B-cell type ALL. The T cell type often presents as a lymphoma with a mediastinal mass [6, 10, 16].

2.10.2 AML

Patients who present with AML will also have symptoms of bone marrow failure; anaemia and thrombocytopenia. The WBC's can range from subnormal to highly elevated.

The morphology will show myeloblasts from either B or T cell origin, often with Auer Rods. Detection of leukemic cells is done by Romanowsky stain,

sometimes in addition with Myeloperoxidase, Sudan Black, PAS (periodic acid-schiff), NSE (non-specific esterase) or acid phosphatase. The criterion for diagnosis of AML is 20% or more blasts in the BM (according to WHO).

The immunophenotyping will show leukemic expression of CD13 and CD33 antigens. M7 always show CD41 and CD42 positivity.

There are several different translocations, but the most consistent is probably M3 (15; 17) (q22; q22). This type has abnormal promyelocytes predominance and is associated with disseminated intravascular coagulation. AML M3 follows its own treatment protocol [6, 10].

2.11 Treatment

2.11.1 ALL

The treatment of ALL is chemotherapy. All paediatric patients in the Nordic countries receive the same treatment from the NOPHO ALL 2008 protocol. This protocol is again based on NOPHO ALL-92 and NOPHO ALL-2000. The treatment protocol lasts for two and a half year and is subdivided into: induction, consolidation and maintenance phase. A combination of vincristine, prednisolone, antracyclines, L-asparaginase and methotrexate is used. The goal is of course to cure the patient, but there is balance between excessive toxicity and maintaining a high cure rate, neither overtreat nor undertreat. There is a variation in treatment dependent on the differing risk groups.

The induction phase lasts for six week (according to Einungbrekke Amanda Jensen's medical Journal, 1998~2009, founded by Hospital in Telemark and Oslo University Hospital) and the aim is to eradicate more than 99% of the blasts during this phase. In the induction phase, there is a combination of glucocorticoids (prednisone, prednisolone and dexamethasone), Vincristine, Antracyclines, Asparaginase and Methotrexate. Some of the therapy is directed directly to CNS, often as intrathecal administration of methotrexate. On the other hand, dexamethasone has

an indirect effect on CNS as it penetrates the BBB well. The patient can be considered for the consolidation phase once normal haematopoiesis is restored. The chemotherapy prescribed at this stage involves high dosage of Methotrexate, mercaptopurine, vincristine and high doses with asparaginase. Allogenic stem cell transplantation can be a choice in very high-risk patients or those with poor response to treatment. Maintenance phase continues for two and half a half years. There is a combination of 6-mercaptopurine and methotrexate in tablet form, and also reinductions with vincristine/dexamethasone alternately with methotrexate. It exists own protocols for infant-ALL and Philadelphia-chromosome-positive ALL. As already stated, the future treatment of leukemia will focus more on reducing the toxic side effect of each component drug such as, for example, Doxorubicin [1, 4, 10, 15].

2.11.2 AML

For AML NOPHO-DBH-AML 2012-protocol is used. A combination of chemotherapy, antracyclines, cytarabin, etoposid is used. In AML, we divide into standard risk or high risk, according to how they respond to the first treatment. Patients in the high-risk group are candidates for stem cell transplantation in first remission. FAB M3 should be treated according to international APL protocol with all-trans-retinoic acid [1, 4, 10, 15].

2.11.3 MRD

Minimal residual disease is used to measure treatment response in patients, and to detect possible relapses. This is a newer method and can especially help patients with poorer prognosis. MRD is measured by flow cytometers and PCR [17].

Flow-cytometer is based on the detection of antigen expressed in the leukemic cells such as Tdt (Fig. 7) and CD10. There has been seen a correlation between MRD levels during clinical remission and treatment outcome. Acute leukemia is considered to be in remission when there is < 5% blasts in the BM. With early detection of relapse it is possible to change the

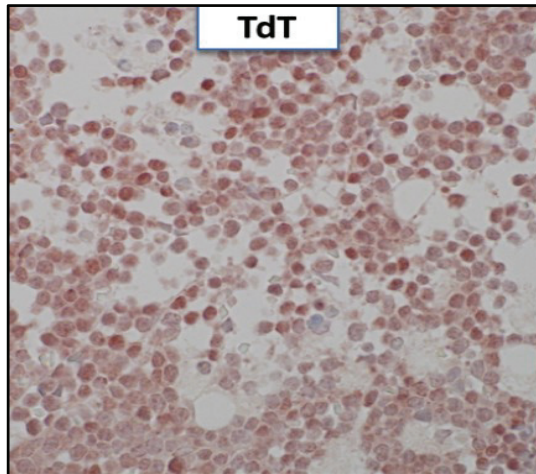


Fig. 7 Tdt. Photos from the register of Prof. Plank, Department of Pathology in Martin, Slovakia. Accessed April 2015.

treatment strategy, and possibly improve the cure rate [1, 4, 6, 18].

2.11.4 Stem Cell Transplantation

BM transplantation from a suitable allogeneic donor can cure an otherwise incurable leukemia. For ALL allogeneic hematopoietic stem cell transplantation should be carefully selected. It is indicated in very high-risk patients and those with poor treatment response. Some subtypes of ALL, such as PH+ ALL, have been shown to benefit from transplantation. HLA typing of the donor to find the most suitable match is very important for the result and to avoid GVHD. Allogeneic stem cell transplantation in AML patients is used more compared to ALL patients. In the Nordic countries, it is indicated for children with high-risk criteria in remission, and for second remission. Long-term complications develop more often in paediatric patients treated with Bone marrow transplantation compared to those receiving just chemotherapy. So this is of course something to take into consideration when considering the suitability of stem cell transplantation [4, 10, 15, 19].

2.12 Side Effects during Treatment

Adverse reactions of AML and ALL are quite similar, due to many of the same chemotherapeutic drugs. The treatment is very intense though and it is

crucial with supportive therapy to help the child through this year with chemotherapy. Supportive therapy will also have a positive effect on side effects, the side effects will be reduced and thus lead to a better life during and after treatment.

Doxorubicin/adriamycin will very often give adverse reactions as leucopenia, neutropenia, anemia, thrombocytopenia, inflammations in GIT, diarrhea, nausea, vomiting, hair loss, infection, decreased appetite, decreased ejection fraction and congestive heart failure. The Norwegian Health care recommends regular check ups with echocardiography during and after treatment with Doxorubicin [20].

Vincristine often gives side effects as alopecia, muscle weakness, muscle atrophy, loss of tendon reflexes, leg pain, jaw pain, paresthesia neuritis pain and leucopenia [21].

Methotrexate will give leukopenia, neutropenia, thrombocytopenia, anemia, stomatitis, nausea, vomiting, infections, alopecia, decreased kidney function and fatigue. Calcium folinat (leukovorin) injection is used as an antagonist to prevent adverse reactions [22].

Prednisolone will give side effects in the form of Cushing symptoms, skin atrophy, decreased wound healing, hypokalemia, sodium retention, muscle atrophy, growth retardation. It will inhibit excretion of ACTH and cortisone [23].

Asparaginase can give allergy, anaphylactic reaction, thromboembolic complications and hemorrhagic pancreatitis [24].

Cytarabin often gives infections, BM suppression in form of thrombocytopenia, anemia, megaloblastic anemia leucopenia and decreased number of reticulocytes. Other common adverse reactions are oral/anal infections or ulcerations, diarrhea, nausea, vomiting and itching [4, 24, 25].

2.13 Side Effects Later in Life and Follow Up Care

Childhood cancers are different compared to cancer in adults. A child is under development when he/she

gets the disease, and the cancer and chemotherapy can damage the maturation process. They have also longer life expectancy compared to adults and therefore more time for side effect to occur.

In recent past years, side effects in children have not been fully focused upon as understanding the main concern has been curing the patient. Fortunately, in most cases, this was successful. However, the intense treatment creates additional problems in later life with which the patient has to cope, sometimes for the rest of their lives. Currently, most children are monitored up to eighteen years of age but thereafter have to contact their GP should they become unwell. GP's are not cancer specialists and are therefore sometimes unaware of the many side effects resulting from different chemotherapeutic drugs that have been administered to the patient.

Overall childhood leukemia is quite rare, therefore it is quite difficult to find sufficient cases to study and many childhood cancer survivors are now in adult hood and devoid of any follow up consultations. Side effects after acute leukemia vary between individual risk groups and is consequently dose related. Most of the survivors will experience changes, some to a greater or lesser degree. There could be hormonal changes, the fertility can be reduced, Heart function can be decreased, fatigue, problems with the musculoskeletal system, concentration problems, psychological difficulties and secondary malignancy.

The fertility questions is a difficult one, both the disease itself and the treatment can give reduced fertility. The ovaries in girls are mostly at risk if the treatment is received at post-pubertal age.

Cardiotoxicity is recognised complication of doxorubicin treatment. The chemotherapy is believed to impair the myocardial growth in a dose related fashion. Patients treated for ALL will have an echocardiography examination on the last check up. An AML patient on the other hand will have echocardiography examinations during the whole treatment period. In the new guidelines from

Helsedirektoratet, they recommend all patients treated for acute leukaemia to go for regular check up with echocardiography also after treatment and in adult life.

Problems with musculoskeletal system may appear as growth disturbances, osteoporosis, secondary tumors and reduced bone density.

Secondary malignancy may be the survivors biggest fear. They have 3~10 times higher risk of developing malignancy compared to the rest of the population. The chemotherapy can damage the genetic material in the nucleus, and a new malignancy can develop.

Fatigue is a newer term in the cancer context. After treatment, the patient can experience chronic tiredness and a noticeable change in energy levels but this will vary from patient to patient [1].

3. Practical Part

3.1 Case Record in November 1998

A 7-year-old girl is presented to the ER with fever and abdominal pain. They suspect appendicitis. She has had abdominal pain on and off for the last two months, and complained about leg pain the last year. At the ER, she is pale and weak, but in an overall good condition. The vital parameters are normal. The only pathological findings are lymphadenitis at the neck and a systolic murmur Grade 2. The blood tests show CRP: 18, WBC: 2.0, Hb: 8.1, Tbc: 85 (mild pancytopenia). The assessment is that it seems viral characterized. She is admitted to the paediatric department.

Two days later, they take a new blood test: Hb: 7.2, WBC: 2.0, Tbc: 90, CRP: 44, Reticulocytes: 0.3. The peripheral blood smear shows a low WBC's count, granulocytes 45%, and a predominance of immature mononuclear cells. The same day in anaesthesia, a BM puncture from right crista shows a very monotonous picture of uniform blasts, 90% nucleated.

Two days later, she is transferred to a regional hospital for further investigation and a new BM biopsy. This shows the same picture of monotonous lymphoblast. An immunological examination displays that all bone marrow cells emanate from pre B-cell

stadium. She got the diagnosis acute lymphoblastic leukemia standard risk group.

3.2 Diagnosis

Fig. 8 shows BM from this case record.

3.3 Immunophenotyping

BM biopsy is dated November 11, 1998. This is the result from the immunophenotyping, a diagnostic method performed on cells from the BM (Table 2).

3.3.1 Assessment of Bone Marrow Biopsy

Seen in bone marrow is a nearly uniform population of small to medium sized cells with low side scatter.

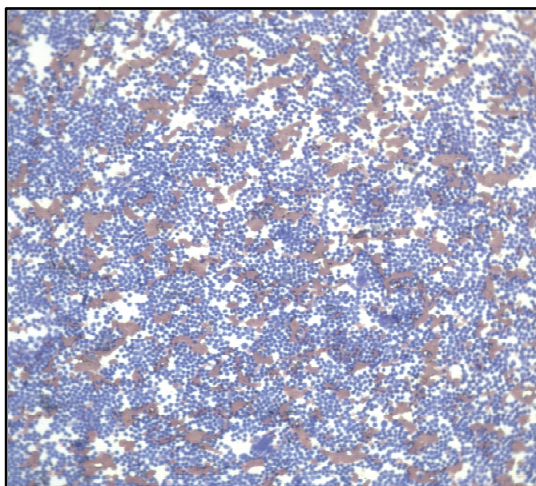
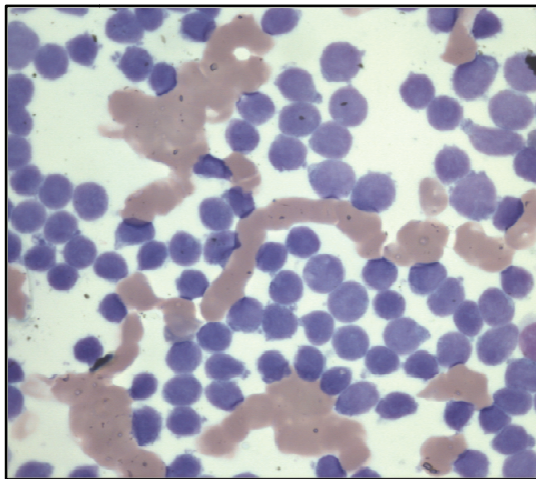


Fig. 8 BM from November 1998. Deadly monotomy, a tedious picture of small blue lymphoblasts, barely other cells visible. The red cells are compared clumping RBC's. Einungbrekke Amanda Jensen's Personal Medical Journal, 1998–2009, Hospital in Telemark and Oslo University Hospital.

Table 2 Antibodies against the BM.

Items	Value
B cell-line	
CD10 (a-CALLA, 552/36)	72
CD19 (HD37 PE)	96
CD20 (B-Ly1)	2
CD24 (CLB-134)	96
CD37 (IGB1)	
CD38 (OKT10)	
T cell-line	
CD7 (DK24)	2
CD5 (UCHT-2)	72
CD2 (MT910)	
CD1 (OKT 6)	
CD3 (UCHT-1)	2
CD4 (MT 310)	
CD8 (DK25)	
TCR alpha/beta (T-cell SCIENCES)	
TCR g/d (T-cell diagn.)	
Pan myeloid	
CD13 (WM47)	16
CD33 (WM 44)	1
CD68 (EBM M)	
Various cell types	
HLA-ABC (E2-14)	
HLA-DR (CR3/43)	97
CD34 (HPCA-2)	96
CD45 (LC, T29/33)	91
CD56 (Leu 19)	
CD103 (HML-1)	
Anti-kappa	2
Anti-lambda	
5 a-desmin	
Cytokeratin (AE1/AE3, ICN)	
Monocyte line	
CD14 (TUK4)	1
CD11b (44)	
IgG1	1
Platelets and megakaryocytes-line	
CD41 (ITI-PL2)	
CD42 (ITI-PL1)	
CD42 (ITI-PL1)	<1
Erythroid line	
Glycophorin A (1C10)	3
Antigens close to stem cells	
CD34 (HPCA 2)	
Tdt (aTdt)	
Activation antigens	
CD25 (A-Tac, ACT-1, CD25)	
CD30 (BER-H2)	
CD71 (T58-1)	
Granulocyte line	
CD15 (C3D-1)	1

The cells are positive for CD45 and the B-cells markers CD19, CD24 and HLA-DR.

CD20 and surface immunoglobulin are negative. Stem cell-associated CD34 is positive on all cells. CD10 and CD2 are expressed respectively on 77% and 76% of the cells. Absence of myeloid antigens CD13, CD14, CD15, CD33.

Diagnose: pre B-ALL according to FCA biphenotypic CD19, 10, 24, 34, 45, DR, 2; Standard risk group.

Comments to the immunophenotyping:

As we can see from the diagnosis, they called it a biphenotypic leukemia. This is what we today call aberrant expression of markers from another cell line. So the diagnosis would today most likely be: Pre-B ALL with aberrant expression of CD2 (usually a T-cell marker) but can also be expressed on leukemic B cells. And from the immunophenotyping CD3 and CD7 is both negative, and excludes a possible biphenotypical leukaemia. It is important to remember that this is more than 15 years ago, and the criteria for biphenotypic leukemia have been changed and tightened. It is not enough that the leukemic cells express just one marker from another cell line today.

Leukemia of ambiguous lineage means there is no clear evidence of differentiation along a single lineage (WHO). This type of leukemia is very rare and account for < 4% of all cases. This group of leukemia is today divided into acute undifferentiated leukaemia and Mixed phenotype acute leukemia. Cases that in the past were diagnosed as undifferentiated leukemia may today be diagnosed as leukemia of unusual lineages. And cases that have been reported as Biphenotypic leukemia may today be a clear lymphoid or myeloid leukemia. The reason for this is that the classification has changed the last two decades; today it is based on the clinical features, the immunophenotyping, the morphology and the cytogenetic. And it exists several other criteria before we can call it a mixed phenotype acute leukemia [6].

Tdt is almost always expressed in acute leukemia (even though there exist some exceptions). Tdt is not

mentioned in this immunophenotyping, but it probably was expressed. CD34 was neither mentioned in the immunophenotyping, but mentioned in the result. So they probably forgot to mention Tdt.

3.3.2 Analysis

When a patient is diagnosed with acute leukemia or there is a suspicion for the disease, there is a standard procedure to check for some immunological abnormalities, do a microbiological examination and a cytological examination:

12.11.1998

IgG 13,8 g/l (4,3-13,6) IgA 1,07 g/l (0,35-3,00) IgM 1,77 g/l (0,20-1,70)

Microbiological examination:

11.11.1998

Anti-CMV: Negative Anti-HSV IgG: NEGATIVE
Anti.measelsvirus IgG: Weak positive Anti-VZV IgG: Positive

Cytological examination

19.11.1998

Karyotype:

46, XX

FISH examination

03.12.1998

FISH examination for 12; 21 translocation: Negative

3.4 Treatment

The first day after the diagnosis was set; She got a central venous catheter. The chemotherapy regimen could start already the day after the CVC in-plant. So six days after the admission to ER, chemotherapy after Nordic protocol could start; see theoretical part or NOPHO for the whole protocol. During the treatment period, she underwent regularly blood tests.

After the treatment protocol which lasts two and a half year, regular check-up is started. During the 1st year, there is control each month, 2nd year every 2nd month, 3rd year every 3rd month, 4th year every 4th month, 5th year every 4th or 5th month, 6th year every 6th month, and after this control each year until 18 years of age.

At her last control as an 18-year-old girl, routine cardiac examination after treatment of ALL Echocardiography shows a structural and functionally normal heart. Left ventricle measure diastolic 54.4, set score 0.2 and shortening fraction 30A normal heart at that time.

3.5 Adverse Reactions during Treatment

During the treatment period with chemotherapy, she experienced a lot of side effects. The chemotherapy given is really toxic, and will for sure give some adverse reactions. Not all will experience the same problems, but all will more or less have side effects.

Some of the chemotherapy made her really sick, and especially nausea was a problem. It usually stopped 1~2 days after each cure, and then it start again when a new cure began. Mucositis was another, it occurred frequently when the blood values was low. This led to some nutrition problems.

Vincristine gave her neuromuscular manifestations with sensory and motor disturbances in her legs. She often waked up during the night with big leg pain.

Changed appearance was maybe the worst side effect at that moment. Even though it really does not matter, losing her hair was a big breaker. The steroids gave her typically moon face and an enormous appetite. She could wake up in the middle of the night so enormously hungry. Another side effect of steroids is mood swings, not only affecting the patient but her family as well.

There are infections, due to low WBC's count. So she had to be isolated from the community in some periods. It was strictly forbidden to go to shops, cinema or school.

4. Discussion

Maybe the worst part of being a cancer kid is the life after treatment. When you have to deal with the fact that you once had a life threatening illness, survived and are expected to live a full and happy life thereafter. The truth is however that your every waking moment

nurtures questions such as why me, will my life be normal again, but the darkest thoughts are those about possible secondary malignancy.

I believe we all have a choice about how to deal with life after a really tough and devastating period and the option vary for each and every individual. I actually do not remember how I was told or even how I reacted, probably because I was only seven years old at the time. From the journals I read I did not want to know anything about chemo and treatment at that particular point. But even when you are sick, life for us all goes on and we have to deal with whatever cards you are dealt and believe there will be light at the end of the dark tunnel. And there was a light because 15.05.2001 was my last chemo session. After more than two years in hospital, regular check ups started. Blood tests, talking with doctors, how do you feel etc. was the regular conversation with my doctor. I believe many cancer sufferers feel different after their experience and I know I did but maybe that was because I was so young and face with such a serious diagnosis. When talking about my future with the doctors I always insisted that I would never go to a hospital voluntarily again because I just wanted to forget and live life like my friends, no blood test and medical discussions. As I grew older, I realized that I never will forget, and my cancer story will always be with me. It is not me, but it is a part who I have become.

I was lucky I got standard risk ALL with really good prognosis and few late damage effects compared to others. My ultimate dream is that one day it will be possible to help this patient group by being able to answer questions related to their childhood illness and talk to them about side effects and when they may appear. Many survivors do not know about the side effects that can appear. They have to be able to seek council from understanding and sympathetic professionals about their physical and/or psychological issues later in life. Their worries may not be cancer related but they are still their worries and need to be addressed as a connection could be present. For me, on

a very personal level, there is a much bigger and wider perspective because who cares about possible side effects when you have been given a second chance at life itself. For that chance, I am eternally grateful.

Today, the overall survival rate for ALL is > 80% and for AML 65%. The treatment is very effective and the results are good. Even with such good results there is a long way to go when we think about side effects later in life. A child has longer life expectancy compared to an adult and therefore more time for side effects to occur. Most of the survivors will experience problems, some to a greater or lesser degree. There could be psychological difficulties, hormonal changes, the fertility can be reduced, heart function can be decreased, fatigue, problems with the musculoskeletal system, concentration problems and the worst of them all secondary malignancy. As already stated, the focus has changed somewhat the last years due to more awareness on side effects. I think the focus in the coming years will be more related to possible side effects after treatment and to make as few complications as possible after chemotherapy treatment.

5. Conclusions

Topic of this thesis was acute leukemia in children. Through study of literature and my own case record of ALL, I gained knowledge about this disease. It made me more aware than ever, not only of the though treatment a child has to undergo, but also just how much progress has been made in the diagnosis and treatment of leukemia.

The aim of my diploma thesis was to focus primarily on side effects and follow up care after treatment. To date, we have come a long way in the treatment of paediatric leukemia as can be seen from the result statistics. Modern techniques enable the early and rapid diagnosis of the disease and with high doses of chemotherapy it is possible to cure almost all diagnosed acute leukemia. However, such high doses can result in side effects later in life and although we

monitor patients up to the age of eighteen there is an urgent need for a special department where consultants, who are fully conversant with the disease and the subsequent side effects are available, to whom such people can go as opposed to a GP who may or may not be so knowledgeable. Let's hope it can be introduced a follow up program to prevent complications for all affected patients. This must be the next achievement in the field of paediatric oncology, and will definitively give this patient group a better life and less side effects.

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