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Minimising the Long-Term Adverse Effects of Childhood Leukaemia Therapy

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Abstract

Malignancies in childhood occur with an incidence of 13–14 per 100 000 children under the age of 15 years. Acute lymphoblastic leukaemia with an incidence of 29% is the most common paediatric malignancy, whereas acute myeloid leukaemias account for about 5%. The treatment of acute leukaemias consists of sequential therapy cycles (induction, consolidation, intensification, maintenance therapy) with different cytostatic drugs over a time period of up to 1.5–3 years. Over the last 25 years of clinical trials, a significant rise in the rate of complete remissions as well as an increase in long-term survival has been achieved. Therefore, growing attention is now focused on the long-term effects of antileukaemic treatment.

Several cytostatic drugs administered in the treatment of acute leukaemia in childhood are known to cause long-term adverse effects. Anthracyclines may induce chronic cardiotoxicity, alkylating agents are likely to cause gonadal damage and secondary malignancies and the use of glucocorticoids may cause osteonecrosis. Most of the long-term adverse effects have not been analysed systematically.

Approaches to minimising long-term adverse effects without jeopardising outcome have included: (i) the design of new drugs such as a liposomal formulation of anthracyclines, the development of anthracycline-derivates with lower toxicity, the development of cardioprotective agents or, more recently, the use of targeted therapy; (ii) alternative administration schedules like continuous infusion or timed sequential therapy; and (iii) risk group stratification by the monitoring of minimal residual disease.

Several attempts have been made to minimise the cardiotoxicity of anthracyclines: decreasing concentrations delivered to the myocardium by either prolonging infusion time or using liposomal formulated anthracyclines or less cardiotoxic analogues, or the additional administration of cardioprotective agents. The advantage of these approaches is still controversial, but there are ongoing clinical trials to evaluate the long-term effects. The use of new diagnostic methods, such as diagnosis of minimal residual disease, which allow reduction or optimisation of dose, offer potential advantages compared with conventional treatment in terms of reducing the risk of severe long-term adverse effects. Most options for minimising long-term adverse effects have resulted from theoretical models and *in vitro* studies, but only some of the modalities such as the use of dexrazoxane, the continuous infusion of anthracyclines or timed sequential therapy, have been evaluated in prospective, randomised studies in patients. Future approaches to predict severe toxicity may be based upon pharmacogenetics and gene profiling.

Malignancies in childhood occur with an incidence of 13–14 per 100 000 children under the age of 15 years. Acute lymphoblastic leukaemia (ALL) with an incidence of 29% is the most common paediatric malignancy, whereas acute myeloid leukaemias (AML) account for about 5%.[1] The treatment of acute leukaemias consists of sequential therapy cycles (induction, consolidation, intensification, maintenance therapy) with different cytostatic drugs over a time period of up to 1.5–3 years.[2]

Over the last 25 years of clinical trials, a significant rise in the rate of complete remission (CR) as well as an increase in long-term survival has been achieved in children with leukaemia. For instance, 5-year event-free survival (EFS) has increased in AML from 38 (AML-BFM [Berlin-Frankfurt-Münster] 1978) to 49% (AML-BFM 1993)[3,4]

and in ALL from 68 (ALL-BFM 1981) to 78% (ALL-BFM 1990).[5] Therefore, growing attention is focused on the long-term effects of antileukaemic treatment.

Several cytostatic drugs are known to cause severe long-term adverse effects: anthracyclines may lead to cardiotoxicity, alkylating agents might be responsible for gonadal damage and may induce secondary malignancies, and glucocorticoids are associated with the occurrence of osteonecrosis. The administration of high-dose methotrexate, high-dose cytarabine or L-asparaginase may cause CNS damage.

As many of these effects have been found to correlate with the administered dose, the recording and evaluation of long-term adverse effects has become more and more important for further trials focussing on a reduction of chemotherapy intensity in entities with an excellent outcome.

In the following review, long-term adverse effects caused by cytostatic drugs and efforts to minimise them will be discussed, whereas those effects caused by radiation therapy and stem cell transplantation are excluded.

1. Cytostatic Drugs: Range of Application and Adverse Effects

1.1 Alkylating Agents

Cyclophosphamide and its synthetic analog ifosfamide are alkylating agents of the oxazaphosphorine group. They are related to the nitrogen mustards, which cause death of proliferating cells. Both drugs are used for the induction of ALL treatment as well as for consolidation in AML therapy. The active metabolites phosphoramide mustard and isophosphoramide mustard alkylate DNA and cause DNA cross-linking whereby cell division is blocked. Acrolein, which is concurrently generated by metabolism of both cyclophosphamide and isosfamide, is responsible for the urotoxic effect which occurs in about 15% of all patients and manifests in haemorrhagic cystitis, fibrosis of the urinary bladder and haematuria which may be due to chronic glomerular and proximal tubular toxicity resembling Fanconi-like syndrome.[6-9] The United Kingdom Children's Cancer Study Group (UKCCSG) conducted a multicentre study to evaluate nephrotoxicity associated with ifosfamide. Glomerular and tubular toxicity, occurring in 78% of 76 evaluable patients, correlated significantly with higher doses of ifosfamide.[9]

Furthermore, cyclophosphamide is known to cause primary gonadal damage by interfering with oogenesis and spermatogenesis and can adversely affect the reproductive ability of long-term leukaemia survivors in a dose- and duration-dependent manner. The risk of developing permanent azoospermia after chemotherapy is increased after relatively low cumulative doses (<6 mg/m^2) of cyclophosphamide. Interestingly, girls are more resistant to damage and there is high interindividual variance.[10,11] Cyclophosphamide-induced sterility appears to depend on the dose, the duration of therapy and the state of gonadal function at the time of treatment.[12]

Cardiotoxicity has been observed in some patients who have received high-dose cyclophosphamide,[13-15] mainly in combination with radiation,[16,17] but no causal relationship could be established. After treatment with cyclophosphamide the risk to develop a secondary malignancy, mainly AML/myelodysplastic syndrome (MDS), is increased.[18-21]

1.2 Anthracyclines

The cytotoxic anthracycline agents doxorubicin, daunorubicin and idarubicin are used in the treatment of childhood AML and ALL. They intercalate with the DNA double helix and thus inhibit DNA replication and the action of DNA and RNA polymerases. In addition, the interaction with topoisomerase II seems to be an important mechanism of anthracycline-induced cytotoxicity. By cell cycle analysis, it could be shown, that daunorubicin induces concentration-dependent G2/M arrest, apoptosis and necrosis,[22] and that doxorubicin-mediated apoptosis requires activation of p53 and caspases 9 and 3.[23] The main mechanism probably consists of an enzymatic reduction of the anthracyclines leading to highly re-

active OH-radicals and finally morphologic changes of the myocardium.[24-26] The rare, dose-independent acute cardiotoxicity, which may occur during therapy, can cause transient tachycardias, atrioventricular and branch blocks and nonspecific ECG changes.[27] Chronic cardiac toxicity, which may occur months or years after therapy and manifests in tachycardia, arrhythmia or cardiomyopathy, can cause congestive heart failure or death.

The main limiting factor for using anthracyclines is dose-dependent cardiotoxicity (such as ventricular arrhythmia or congestive heart failure) which is cumulative (rapidly increasing at cumulative doses above 350–400 mg/m^2).[28-32] Cardiotoxicity may be increased by other cytostatic drugs such cyclophosphamide or ifosfamide. Other factors that may increase the risk of cardiac adverse effects are dose intensity, female sex and young age at diagnosis.[33,34] The occurrence of acute cardiotoxicity has been found to be an important risk factor for developing late cardiotoxicity.[35]

1.3 Mitoxantrone and Amsacrine

Mitoxantrone and amsacrine work by the same mechanism of action as the anthracyclines: intercalation of DNA and blockage of topoisomerase II. However, radicals seem not to be involved in the cytotoxic effect. The assumed dose ratio of daunorubicin to mitoxantrone concerning both efficacy and toxicity is 5 : 1.[36] In comparison to anthracyclines, the risk of cardiotoxicity is lower.[37]

1.4 Epipodophyllotoxins

Etoposide is a semi-synthetic derivative of podophyllotoxin, which is used for remission induction and intensification in the treatment of AML. The cytotoxic effect on the cell cycle blocks during the S and G2 phase. Single- and double-strand breaks caused by etoposide in cellular DNA are generally considered as the initial event which leads to cell death; the DNA strand breaks result from stabilisation of the cleavable complex of topoisomerase II-DNA with DNA by etoposide.[38]

Cases of secondary AML, mainly monocytic or myelomonocytic, or other malignancies associated with etoposide have been frequently reported.[39-44] The risk is increased with a cumulative dose >2 g/m^2.[45] Nevertheless, it is difficult to identify a single agent as mainly responsible for inducing secondary malignancies. The occurrence of secondary malignant neoplasms has been suggested to be associated with the use of etoposide, intensive antimetabolite therapy and the use of alkylating agents.

1.5 Antimetabolites

Antimetabolites displace natural metabolites either by forming non-functional macromolecules (cytarabine, 6-thioguanine, 6-mercaptopurine, fludarabine) or by blocking enzymes (methotrexate). In both cases, metabolism and cell division are disrupted. The mechanism of action shows that the effects of antimetabolites are unspecific to all fast dividing cells. Consequently, these are highly toxic drugs.

Methotrexate is a competitive antagonist of folic acid. It has a 10^6 times higher affinity for the enzyme dihydro folic acid reductase than its natural substrate. As a result, the folic acid-dependent synthesis of thymidine and purines is impeded. Methotrexate may be used intravenously for systemic or intrathecally for CNS-directed treatment. For high dose therapy, it is thought that malignant cells will be attacked prior to healthy body cells. Therefore, the application of the antidote folinic acid is essential to protect non-malignant cells from destruction. Adverse effects include nausea, mucositis and diarrhoea. Long-term therapy with high cumulative doses of methotrexate (20–135 g/m^2) is known to cause osteopathy by intracellular accumulation of methotrexate and formation of methotrexate-polyglutamates.[46]

Cytarabine, 6-thioguanine, 6-mercaptopurine and fludarabine are analogues of the pyrimidine and the purine bases. They interfere with the DNA synthesis by blocking essential enzymes (polymerase II) or by replacing the original elements. As a consequence, DNA replication is disrupted because of chromosomal damage or chromatoid breaks. The cytarabine syndrome is characterised by the simultaneous occurrence of fever, myalgia,

bone pain, conjunctivitis and malaise, usually 6–12 hours following drug administration. By the preventive administration of corticosteroids, this syndrome can be impeded. High doses of cytarabine may cause a syndrome of sudden respiratory distress, rapidly progressing to pulmonary oedema and cardiomegaly. Also, cases of cardiomyopathy have been reported after the combination of high-dose cytarabine and cyclophosphamide when used for bone-marrow transplant conditioning.

6-Mercaptopurine is known to cause primary dose-limiting hepatotoxicity including intrahepatic cholestasis and parenchymal cell necrosis which can occur with any dosage, but seems to occur with more frequency when doses of 2.5 mg/kg/day are exceeded.[47] In fludarabine recipients a reduction in CD4+ lymphocytes may be associated with the increased incidence of fever and opportunistic infections. Nausea and vomiting have also been commonly reported, but these are generally mild to moderate in severity. Reversible neurotoxicity has also been occasionally reported.[48]

1.6 Glucocorticoids

The glucocorticoids prednisone and dexamethasone are the most important drugs for remission induction in ALL. They have an anti-proliferative and differentiation-inducing effect and also induce apoptosis in malignant lymphatic cells. Due to their preference for lymphoblasts, they cause rapid reduction of the leukaemic cell burden with minimal myelosuppression. The well-known adverse effects of a systemic use of glucocorticoids for longer than 2 weeks include disturbances in fluid balance and electrolytes, musculoskeletal effects such as osteoporosis and steroid myopathy, dermatological disorders, endocrine effects like the development of cushingoid state, suppression of growth or manifestation of diabetes mellitus and immunosuppression.

Furthermore, dexamethasone as well as prednisone may cause avascular necrosis (AVN) as a chronic complication of leukaemia treatment. While the mechanism of action is still unknown, the risk of AVN has been correlated to the dose and duration of steroid exposure. Adolescents may be more susceptible to developing AVN than prepubertal children, possibly because of epiphyseal closure, which leads to increased intraosseous pressure in occluded bone. Also glucocorticoid-induced fat emboli which lead to blockage of subchondral arteries as well as arterial occlusion caused by steroid-induced coagulation abnormalities have been reported. Dexamethasone, in contrast to prednisone, may increase the risk of neurocognitive late effects in children treated for ALL.[49]

Whereas glucocorticoids are suggested as the main pathogenetic factor for the development of osteonecrosis,[50,51] other cytostatic drugs such as cyclophosphamide[52,53] and even leukaemia itself may also cause, or predispose for, osteonecrosis.[54] The occurrence of osteonecrosis is supposed to be higher in older children (>10 years), in patients receiving two courses of dexamethasone versus one course and in patients treated with dexamethasone (as compared with prednisone), respectively.[55,56] The influence of either female or male sex on the occurrence of fractures and osteonecrosis is discussed controversially.

1.7 Vinca Alkaloids

Cytostatic drugs like vincristine and vindesine are alkaloids obtained from vinca minor, a common herb. Together with corticosteroids they build the basis for ALL remission induction treatment. They specifically interact with tubule, a protein of the microtubuli in the mitotic spindle, which induces an arrest of dividing cells at the metaphase state. Because of their relatively low toxicity for the bone marrow, they are often used in a combined polychemotherapy. Vincristine is used for induction and intensification therapy in children with ALL and for consolidation of AML treatment.

Dose-limiting toxicities are frequent peripheral neuropathies. These adverse effects may start with sensory impairment and paresthesia and possibly go on to neuritic pain and motor difficulties.

1.8 L-Asparaginase/Pegaspargase

The enzyme L-asparaginase catalyses the desamination from L-asparagine to L-aspartic acid. It

exerts a highly specific activity against lymphoblasts, because they are unable to form L-asparagine, which is essential for cell division.

Many patients produce antibodies against the enzyme L-asparaginase. This may on the one hand be due to hypersensitivity reactions, which occur in 25–30% of the patients, and, on the other hand, be due to the inactivation of the drug. Acute adverse effects of L-asparaginase therapy are caused by the inhibition of protein synthesis and include hyperglycaemia secondary to hypoinsulinaemia, hypolipoproteinaemia and hypoalbuminaemia. Deficiencies and imbalances in coagulation factors may lead to bleeding and/or thrombosis and in 1–2% of patients to the occurrence of intracranial haemorrhage or thrombosis.[57,58] Pancreatitis, hepatic dysfunction and neurological dysfunction have been reported in 1–2% of patients.[59]

The chemical attachment of polyethylene glycole (PEG) to L-asparaginase (pegaspargase, PEG-L-asparaginase) leads to a 6-fold increased half-life and decreased plasma clearance. The main advantage is the highly decreased risk of immunological reactions – even in patients who are immunised to the native enzyme – whereas efficacy and toxicity are not influenced.[60,61]

1.9 All-Trans Retinoic Acid

All-trans retinoic acid (ATRA) is a highly specific and effective drug for the remission induction of acute promyelocytic leukaemia (APL; AML FAB [French-American-British classification] M3) by cell differentiation. The underlying molecular pathogenesis of APL is explained by the reduced retinoic acid sensitivity of a nuclear receptor corepressor binding to the fusion protein promyelocytic leukaemia gene-retinoic acid receptor-α (PML-RARα). This fusion protein inhibits the dissociation of the histone deacetylase corepressor complex. As the ATRA sensitivity of the corepressor association with the PML-RARα is lower than with the wild type RARα, pharmacological concentrations of ATRA enable the corepressor dissociation, the association of the coactivator SRC-1 (steroid receptor coactivator-1) with histone acetylation activity and thereby further transcription and differentiation.[62]

Since ATRA is a natural metabolite of retinole, the adverse effects mainly include symptoms of hypervitaminosis A. Severe adverse effects like retinoic-acid syndrome, a complex of fever, capillary leakage, hyperleucocytosis, leucocyte organ infiltration and pseudotumour cerebri were responsible for therapy-related mortality and morbidity in adults and children.

1.10 CNS-Directed Treatment

Treatment or prophylaxis of CNS involvement consists of the intrathecal administration of cytarabine and/or methotrexate and/or prednisone and/or hydrocortisone. The benefit of cranial irradiation for prophylaxis is controversial, whereas irradiation in children and adolescents with initial CNS involvement is necessary.[63]

CNS-directed treatment – intrathecal chemotherapy and/or irradiation – may be associated with acute (headache, nausea and vomiting) and subacute (somnolence, lethargy, anorexia, fever and irritability) neurotoxic reactions. Both, chemotherapy and irradiation may cause impairment of endocrine reproductive function by either direct damage to the gonads or damage to the hypothalamic-pituitary axis.[12,64] By contrast, reduction of linear growth and of subsequent final height seem to be caused by cranial irradiation or total body irradiation.[10,65]

Concerning neuropsychological function and neurotoxicity, there are several evaluations and prospective studies, which compare long-term adverse effects of intrathecal chemotherapy versus irradiation with controversial results. While some studies that show comparable decreases in neuropsychological function,[66,67] it has been reported that significant neuropsychological impairment was only found in those children having received irradiation, whereas intrathecal or systemic chemotherapy did not lead to a cognitive deficit.[68]

2. Clinical Trials

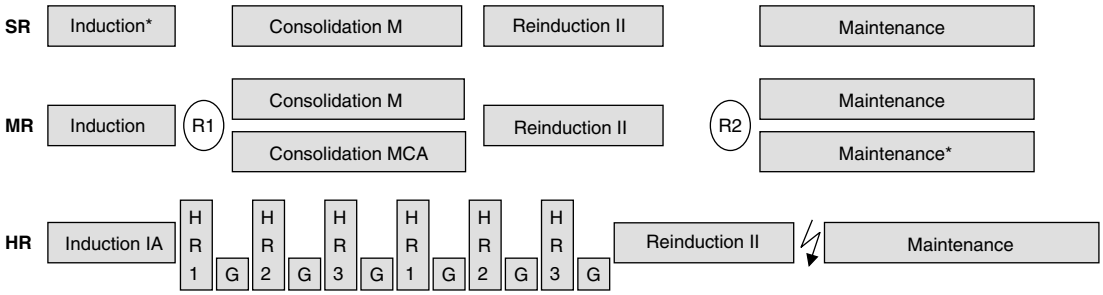
Recent studies of paediatric ALL and AML have been conducted by the 'Associazione Italiana

Ematologia Oncologia Paediatrica' (AIEOP), the German 'Berlin-Frankfurt-Münster' (BFM) group , the US-American 'Children's Cancer Group' (CCG), the 'Dutch Childhood Leukaemia Study Group' (DCLSG), the US-American 'Dana-Farber Cancer Institute' group (DFCI), the 'French ALL study group' (FRALLE), the British 'Medical Research Council' group (MRC), the 'Nordic Society of Paediatric Haematology and Oncology' (NOPHO), the US-American Pediatric Oncology Group (POG), the French 'Society of Paediatric Haematology and Oncology' (SHIP) and the 'St. Jude Children's Research Hospital' (SJCRH).[69-83]

The following chapter includes results and documented long-term adverse effects of recently studied treatment protocols for childhood leukaemia. Regarding the comparison of these trials, it has to be considered that there may be differences concerning patient population, risk group stratification and supportive care as well as the period of time over which the studies were conducted.

2.1 Acute Lymphoblastic Leukaemia

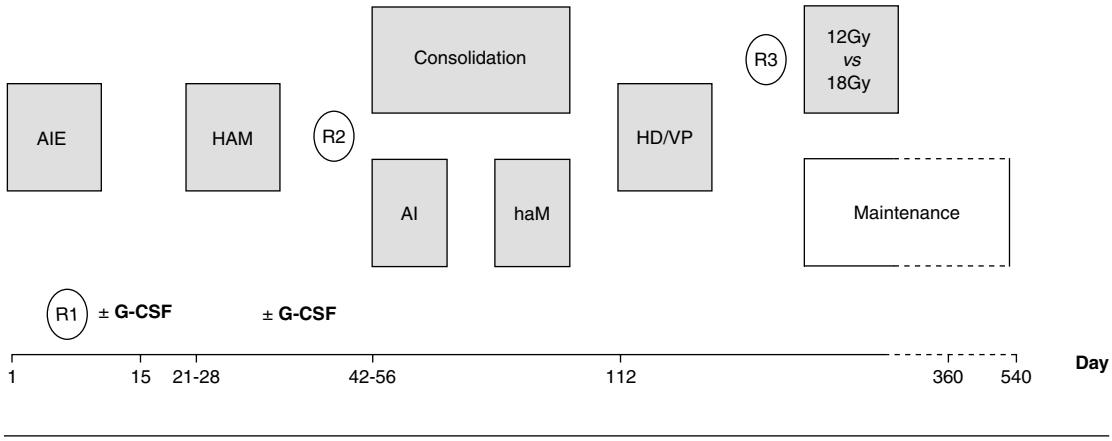
Compared with AML, ALL is a more homogeneous and biologically well investigated disease of childhood. Prognostic factors, such as response to prednisone, age, white blood cell count or chromosomal changes have been identified and can thus be used for treatment stratification. The treatment arms for the different risk groups differ more



SR: standard risk MR: medium risk HR: high risk
R: randomisation

Induction*:	Pred (PO), VCR, DNR (2 x 30 mg/m²/day), l-asp, CP, Ara-C, MTX (IV), MTX (IT)
Induction:	Pred (PO), VCR, DNR (4 x 30 mg/m²/day), l-asp, CP, Ara-C, MTX (IV), MTX (IT)
Induction IA:	Pred ((PO), VCR, DNR, l-asp, MTX (IT)
Consolidation M:	6-MP (PO), HD-MTX, MTX (IT)
Consolidation MCA:	6-MP (PO), LD-Ara-C, HD-MTX, MTX (IT)
Reinduction II:	Dexa (PO), VCR, ADR, l-asp, CP, Ara-C, 6-TG (PO), MTX (IT)
HR1:	Dexa (PO), VCR, HD-Ara-C, HD-MTX, CP, l-asp, MTX (IT), Ara-C (IT), Pred (IT)
HR2:	Dexa (PO), VDS, HD-MTX, Ifo, l-asp, MTX (IT), Ara-C (IT), Pred (IT)
HR3:	Dexa (PO), HD-Ara-C, VP-16, l-asp, MTX (IT), Ara-C (IT), Pred (IT)
G:	Granulocyte-colony stimulating factor
Maintenance:	6-MP (PO), MTX (PO)
Maintenance*:	6-MP (PO), MTX (PO), VCR, dexa (PO)
↯ :	Cranial irradiation 12 Gy

Fig. 1. Treatment schedule of the German trial ALL-BFM 95 (acute lymphoblastic leukaemia Berlin-Frankfurt-Münster 1995). **6-MP** = 6-mercaptopurine; **6-TG** = 6-thioguanine; **ADR** = doxorubicin; **Ara-C** = cytarabine; **CP** = cyclophosphamide; **Dexa** = dexamethasone; **DNR** = daunorubicin; **HD** = high dose; **Ifo** = ifosfamide; **IT** = intrathecal; **IV** = intravenous; **LD** = low dose; **l-asp** = l-asparaginase; **MTX** = methotrexate; **Pred** = prednisone; **PO** = oral; **VCR** = vincristine; **VDS** = vindesine; **VP-16** = etoposide.



R: randomisation	G-CSF: filgastrim
AIE:	Ara-C, IDR, VP-16, Ara-C (IT)
HAM:	HD-Ara-C, mitox, Ara-C (IT)
AI:	Ara-C, IDR, Ara-C (IT)
haM:	HD-Ara-C, mitox, Ara-C (IT)
Consolidation (phase 1):	pred, 6-TG (PO), VCR, IDR, Ara-C, Ara-C (IT)
Consolidation (phase 2):	6-TG (PO), Ara-C, CP, Ara-C (IT)
HD/VP:	HD-Ara-C, VP-16, Ara-C (IT)
Maintenance:	6-TG (PO), Ara-C, Ara-C (IT)

Fig. 2. Treatment schedule of the German trial AML-BFM 98 (acute myeloid leukaemia Berlin-Frankfurt-Münster 1998). **6-TG** = 6-thioguanine; **Ara-C** = cytarabine; **CP** = cyclophosphamide; **G-CSF** = granulocyte-colony stimulating factor; **HD** = high dose; **IDR** = idarubicin; **IT** = intrathecal; **mitox** = mitoxantrone; **pred** = prednisone; **PO** = oral; **VCR** = vincristine; **VP-16** = etoposide.

within trials than the treatment for the same risk groups differ among trials. To give an example, the treatment schedule of the trial ALL-BFM 95 is shown in figure 1.[77]

2.2 Acute Myeloid Leukaemias

During the last decades, several therapy studies for the treatment of children with AML have been carried out. The treatment schedule of the German AML-BFM 98 trial is shown in figure 2.

As to the most important elements of AML therapy, which are common to almost all studies – cytarabine and the anthracyclines – there are differences regarding the cumulative doses. Single doses of cytostatic drugs are almost identical, whereas cumulative doses show a wide variance (figure 3). The MRC-AML 10 trial uses the highest cumulative dose of anthracyclines (650 mg/m^2), followed by the LAM87 trial of the AIEOP (580 mg/m^2), whereas the other trials use cumulative doses below the known limit of cardiotoxicity (400 mg/m^2). Concerning the cumulative dose of cytarabine, the NOPHO-88 uses the highest dose (70 g/m^2). The trials AML-BFM-93, CCG-2891 and POG 8821 use mean cumulative doses of 38–43 g/m^2, and AIEOP-LAM87, MRC-AML10 and SHIP-LAME89/91 employ low doses of 9–12 g/m^2 cytarabine.

2.3 Results of Clinical Trials

There is a lack of information about long-term adverse effects of polychemotherapy concerning the recent clinical trials for childhood ALL and AML mainly because follow-up time was too short or reporting was inappropriate. There are some reports covering the retrospective evaluation of long-

term adverse effects after childhood leukaemia treatment. Table I summarises the reported second malignancies, cardiotoxicity as well as somatic and neuropsychological sequelae in long-term survivors (≥5 years) of childhood leukaemias. There is a great variability in reported qualitative and quantitative long-term adverse effects: e.g. the incidence of secondary malignancies (varies from 0.1% in children and adolescents treated for ALL by the Swiss Paediatric Oncology Group to up to 9% in childen treated for AML in the SJCRH trial), the impairment of neurocognitive function (51% with learning problems vs no differences in IQ compared with the general population) or pubertal development (normal vs slower).[85] Especially concerning neurocognitive function, the lack of standardised measurement makes it difficult to compare different trials.

Different treatment schedules with different drugs and/or irradiation and/or stem cell transplantation limit comparison of the shown evaluations. In most cases, there was no differentiation of long-term adverse effects between the single agent cytostatic drugs. Nevertheless, children receiving chemotherapy exclusively seem to show lower incidences of somatic or neuropsychological impairment compared with additional irradiation and/or stem cell transplantation.[70]

3. Approaches to Minimise Long-Term Adverse Effects of Childhood Leukaemia Therapy

Intensive polychemotherapy is inevitable for the treatment of childhood leukaemia. Several approaches to minimise the associated risk of inducing long-term adverse effects are being evaluated in ongoing preclinical or clinical trials. The majority of published results to minimise long-term adverse effects were obtained by studies conducted with adults, whereas only a few paediatric trials were executed.

3.1 Designing New Drugs

3.1.1 Liposomal Formulations

The liposomal encapsulation of anthracyclines entails different pharmacokinetic properties which result in increased distribution in tumours, prolonged circulation and reduced free drug concentration. Clinical effects may include increased activity and decreased toxicity of the anthracyclines.[91]

The encapsulation of anthracyclines inside liposomes has been found to reduce acute and

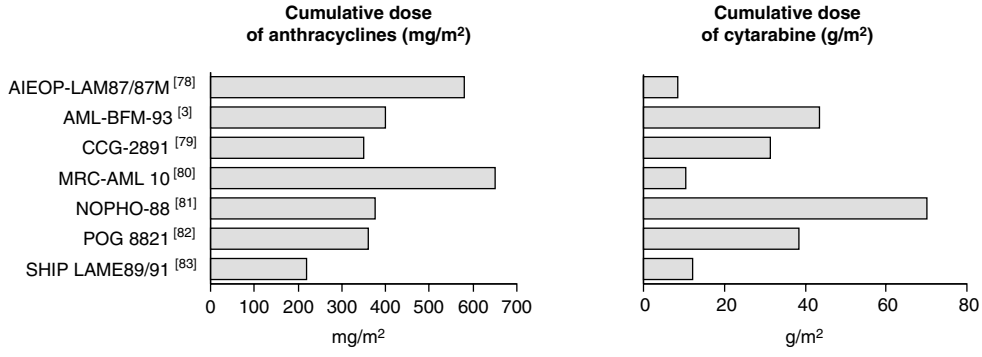


Fig. 3. Cumulative doses of anthracyclines and cytarabine in recent paediatric acute myeloid leukaemia (AML) studies. Doses of idarubicin and mitoxantrone were multiplied by a factor of 5 in order to be comparable to doses of daunorubicin and doxorubicin. This calculation was done assording to the proposals published by the British AML Collaborative Group[84] for the more appropriate basis for comparison of efficacy of different anthracyclines. **AIEOP** = Associazione Italiana Ematologia Oncologia Paediatrica; **BFM** = German 'Berlin-Frankfurt-Münster group'; **CCG** = Children's Cancer Group; **MRC** = British 'Medical Research Council group'; **NOPHO** = 'Nordic Society of Paediatric Haematology and Oncology'; **POG** = US-American Pediatric Oncology Group; **SHIP** = French Society of Paediatric Haematology and Oncology.[3]

Table I. Summary of long-term adverse effects of treatment for childhood leukaemia observed in recent prospective clinical trials and retrospective evaluations

Trial/study group	Patient no. (cancer type) [median follow-up]	Second malignancy	Cardio-toxicity	Somatic/neuro-psychological sequelae	Other long-term adverse effects/comments
Results of prospective clinical trials					
ALL-BFM 90[70]	2300 (ALL) [4.8y]	10 (0.4%)	NA	NA	Comparison between different risk groups (and different treatment) is not yet available
DFCI 91-01[72]	386 (ALL) [5.0y]	NA	NA	NA	Data regarding osteonecrosis were not prospectively collected, but 56 patients (16%) experienced a bone fracture
Retrospective evaluations					
St. Jude Children's Research Hospital[86]	324 (AML); 77 (24%) survived for at least 10y after diagnosis [16.7y]	7 (9%)	5 (6%)	Growth: 24 pts (31%): decreased height Z score	Patients with chemotherapy alone (compared with those with additional irradiation and/or BMT) had a lower incidence of long-term effects such as growth impairment, disorders of reproductive endocrine function and fertility or neurocognitive function
				Mild cognitive deficits: 11 pts (14%)	
				Pubertal development: normal	
Dutch Childhood Leukaemia Study Group[87]	1193 (ALL and AML); 392 (33%) in first CCR for at least 6y after diagnosis [NA]	9 (2%) [in 5 pts in the irradiated area]	Rarely reported	Growth: mean height SDS of boys and girls (≥4y after treatment) decreased	Pulmonary, urogenital, and musculoskeletal toxicity was rarely reported
				Learning problems: 51%	
				Pubertal development: slower than in the average Dutch population	
Swiss Paediatric Oncology Group[88]	150 (ALL); at least 5yrs of survival [10y]	1 (0.1%)	4 (3%)	Growth: 7 (5%); all received cranial radiotherapy	117 pts. (83%): no or minimal late toxicity (grade 0 and 1)
				Severe somatic/ neuro-psychological: 4 (3%)	19 pts. (14%): moderate impairments
				Endocrine: 20 (13%)	No differences in IQ beween ALL survivors and general population, but IQ scores were higher in non-irradiated children
ALL-BFM[89]	5006 (ALL) [5.7y]	52 (1%)	NA	NA	AML n = 16, CNS n = 23, others n = 23
Children's Cancer Group[90]	9720 [NA]	43 (0.4%)	NA	NA	Higher risk for children younger than 5y and those receiving irradiation

ALL = acute lymphoblastic leukaemias; **AML** = acute myeloid leukaemia; **BFM** = German 'Berlin-Frankfurt-Münster' group'; **BMT** = bone marrow transplantation; **CCR** = complete clinical remission; **DFCI** = 'Dana-Farber Cancer Institute' group; **IQ** = intelligence quotient; **NA** = not available.

chronic cardiotoxicity while maintaining anticancer potency in animals and in phase I clinical trials in adults.[92-97] The 50% lethal dose (LD_{50}) was increased from 23 mg/kg for free doxorubicin compared with 44 to 161 mg/kg for liposomal doxorubicin, depending on the preparation.[98] The reduction of cardiac toxicity by liposomal daunorubicin and/or doxorubicin could be attributed to: (i) altered disposition into subcellular compartments; (ii) increased plasma drug exposure to tumour cells; and (iii) significant reduction in the immune suppressive activity.[93] Because of the

lower cardiac toxicity, increased doses of anthracyclines may be administered with subsequently improved treatment efficacy.[98]

At present, liposomal formulations of doxorubicin and daunorubicin are available. Several clinical studies on the use of liposomal daunorubicin or liposomal doxorubicin to reduce chronic heart failure are in progress (see table II). They all show substantial efficacy with clearly decreased acute cardiotoxicity compared with the free form of the drug.[97,99-101] However, with regard to chronic cardiac toxicity, results are not available yet.

3.1.2 Cardioprotective Agents

Many potentially cardioprotective drugs have been evaluated to reduce the cardiotoxicity of anthracyclines: digoxin,[105,106] vitamin E,[105] carnitine,[107] ubidecarenone,[108] acetyl cysteine[109] or corticosteroids,[106] but none of them appears to be effective. Only one agent, dexrazoxane, has proven to protect against cardiotoxicity of doxorubicin and other anthracyclines without affecting their anti-tumour activity.[110-112] The cardioprotective effect of dexrazoxane is thought to be caused by iron chelation following intracellular hydrolysis. This results in a reduction of anthracycline-iron-complexes and the subsequent formation of free radicals.

Several clinical trials were performed to evaluate the cardioprotective effect and the toxicity of dexrazoxane (see table III). They have shown that the combination of anthracyclines with dexrazoxane may protect against anthracycline-induced cardiotoxicity,[113-116] while dexrazoxane does not influence the anticancer activity or other adverse effects of the anthracyclines.[113,114,117] The dose-limiting factor for the use of dexrazoxane is its myelotoxicity. Although the protection from acute cardiac toxicity could be shown in preliminary studies in children and adults, long-term benefit remains unclear.

3.1.3 Derivatives of Lower Cardiotoxicity

The first two anthracyclines, doxorubicin and daunorubicin, differing only by a single hydroxyl group, were developed in the 1960s. Several attempts have subsequently been made to develop analogues of doxorubicin which exhibit lower acute and chronic toxicity and/or increased anti-tumour activity.

Table II. Studies to determine the efficacy and toxicity of liposomal encapsulated anthracyclines

Reference	Drug	Patient no.	Disease	Study design	Aims	Results
Berry et al.[102]	ADR	10 (vs historical control group)	Kaposi sarcoma	Comparison vs historical control group	Evaluation of cardiotoxicity of liposomal ADR	Patients receiving liposomal ADR had significantly lower biopsy scores compared with ADR controls despite higher cumulative doses of anthracycline
Harris et al.[103]	ADR	224	Metastatic breast cancer	Randomised comparison	Comparison of efficacy and toxicity of liposome-encapsulated and conventional doxorubicin	Protocol-defined cardiotoxicity was observed in 13 vs 29% of patients given liposomal or conventional ADR, respectively; median cumulative dose at onset of cardiotoxicity was 785 mg/m^2 liposomal vs 570 mg/m^2 conventional ($p = 0.0001$, hazard ratio 3.56); response rate 26% in both groups
Cortes et al.[99]	DNR	72	Refractory/ recurring AML/MDS	Phase I/II	Effect of liposomal DNR in AML	Cardiotoxicity grade 2: 4 pts. (6%); grade 3 to 4: 4 pts. (6%)
Fassas et al.[104]	DNR	28	Refractory or relapsed AML	Phase I–II	Determination of maximum tolerated dose, early adverse effects and efficacy of liposomal DNR	Well tolerated at all administered levels; two episodes of cardiotoxicity resulting in the death of two patients

ADR = doxorubicin; **AML** = acute myeloid lukaemia; **DNR** = daunorubicin; **MDS** = myelodysplastic syndrome.

Table III. Efficacy and tolerability of dexrazoxane as a cardioprotective agent for anthracycline-induced cardiotoxicity

Reference	Drug	Patient no. (disease)	Study design	Results
Swain et al.[118]	ADR ± DZX	534 (advanced breast cancer)	Multicentre, randomised, double-blind	DZX has a significant cardioprotective effect as measured by noninvasive testing and clinical congestive heart failure
Lopez et al.[113]	Epirubicin ± DZX	95 vs 34 (breast cancer; soft tissue sarcoma)	Randomised, prospective	DZX significantly protects against the development of cardiotoxicity when high single doses of epirubicin are used. Apparently, there was no evidence of an adverse impact of dexrazoxane on antitumour activity
Venturini et al. [114]	Epirubicin ± DZX	160 (breast cancer)	Randomised, controlled trial	Cumulative probability of developing cardiotoxicity was significantly lower in DZX-treated patients than in control patients (p = 0.006; OR, 0.29; 95% CL, 0.09–0.78). Cardiac toxicity, objective response, progression-free survival, and overall survival were similar in both arms

ADR = doxorubicin; **CL** = confidence limit; **DZX** = dexrazoxane; **OR** = odds ratio.

Preclinical and animal data have suggested that idarubicin may be more effective and less cardiotoxic than daunorubicin.[119] However, cardiotoxicity of idarubicin is similar to daunorubicin when given in doses causing equivalent myelotoxicity.[120] Idarubicin was compared with daunorubicin in the randomised AML-BFM 93 trial. At similar toxicity, idarubicin showed better efficacy than daunorubicin, especially an early effect for high risk patients.[3]

Clinical studies with epirubicin indicate an overall activity comparable to doxorubicin. Whereas long-term results are not available yet, current findings suggest that epirubicin may be administered at higher cumulative doses than doxorubicin before cardiotoxicity limits further therapy.[121] However, compared with doxorubicin, the difference in cardiotoxicity in equally effective doses is minimal.[122,123]

Concerning mitoxantrone, which acts mainly through topoisomerase II poisoning, the benefit in balance between cardiotoxicity and antineoplastic effect is undetermined as yet.[124,125] Although cytotoxic efficacy was not higher than that of the two original anthracyclines, some differences in toxicity have been seen.[126]

3.1.4 Targeted Therapy

All of the cytostatic drugs described above do not specifically attack leukaemic blast cells, but also other dividing hematopoietic and non-haematopoietic cells. The development of antibody-targeted cytostatics and radiolabelled antobiotics might lead to safer and possibly more effective treatment than the use of conventional cytostatic agents.[127,128]

Gemtuzumab Ozogamicin

The first FDA-approved agent is an antibody directed against the CD33 antigen, which is commonly expressed on AML blast cells, linked to the cytotoxic calicheamicin (gemtuzumab ozogamicin). *In vivo* and *in vitro* studies showed that gemtuzumab ozogamicin binds specifically and rapidly to CD33+ cells followed by internalisation and subsequent induction of cell death.[129] In a phase II study of 142 patients with CD33+ AML in first relapse, the overall response rate to monotherapy with gemtuzumab ozogamicin was 30%, with a relatively high incidence of myelosuppression, hyperbilirubinaemia and hepatic transaminases, but low incidence of severe mucositis and infections.[130,131] Studies to confirm the clinical benefit are ongoing, but there are also several reports about toxic effects such as hypersensitivity reactions, pulmonary toxicity and hepatotoxicity, especially veno occlusive disease (VOD).[132-137] Preliminary data on the use of gemtuzumab ozogamicin in children with AML suggest good tolerability.[129]

Imatinib Mesylate

Imatinib mesylate, formerly STI571, is an aminopyrimidine derivative which interacts with the ATP-binding site within the kinase domain of ABL and several other tyrosine kinases, including c-KIT, platelet-derived growth factor (PDGF) beta receptor and ARG (tyrosine kinase) resulting in apoptosis of BCR-ABL expressing cells.[138-140] It induces haematological remission in the majority of patients with BCR-ABL tyrosine kinase from the Philadelphia chromosome (Ph+) in chronic myeloid leukaemia (CML),[141,142] but it also has potential for the treatment of other cancers expressing BCR-ABL, including Philadelphia-chromosome-positive acute lymphoblastic leukaemia (Ph+ALL). Adverse effects include nausea, vomiting, myalgia, oedema and diarrhoea. Recently, there have been case reports of splenic rupture after treatment with imatinib mesylate; however, no causal relationship has been proven.[143]

Within all subgroups of ALL, patients with Ph+ALL have the worst prognosis when treated with currently established treatment regimens. In a pilot study it was shown that the administration of imatinib to patients with refractory or relapsed Ph+ALL resulted in a significant anti-leukaemic effect with favourable toxicity profile.[142] However, cure of leukaemia could not have been achieved in the majority of these patients treated with imatinib alone.[144]

Radiolabelled Antibodies

Imatinib mesylate, as an innovative treatment approach, allows specific targeted therapy against the leukaemic kinase BCR/ABL. Theoretically, it only affects leukaemic cells with BCR/ABL without long-term effects on other (healthy) cells. The use of radiolabelled antibodies is based upon the idea of targeted therapy against leukaemic cells expressing specific antigens. Therefore it is possible to specifically target leukaemic cells with reduced damage to healthy cells. By this strategy it might be possible to reduce long-term adverse effects.

Furthermore, approaches of targeted therapy with radiolabelled antibodies have been performed. A pilot study with ^{131}I-labelled anti-CD33 antibody in patients with AML prior to total body irradiation and marrow transplantation was given up because of insufficient targeted radiation.[145] In a phase I study with ^{213}Bi-labelled anti-CD33 antibody, no CR in AML patients could be achieved, even though bone marrow blasts were reduced in 12 of 17 patients. Two studies were performed to evaluate the use of ^{131}I-labelled anti-CD45 antibody in combination with conventional treatment in patients with acute leukaemias (ALL or AML) or MDS receiving marrow transplantation. It was demonstrated that at least twice as much radiation could be delivered to the bone marrow and spleen[146] and that the additional use of targeted radiation might lead to a significantly lower relapse rate.[147]

Results concerning the long-term adverse effects of targeted chemotherapy are not yet available, because of too short follow-up time.

3.2 Dose and Schedules

3.2.1 Continuous Infusion of Anthracyclines

The hypothesis that chronic cardiotoxicity of anthracyclines is mainly associated with the peak dose concentration, whereas the antitumour efficacy is more related to the total drug exposure, measured as area under the plasma concentration-time curve (AUC), led to attempts to prevent anthracycline-induced cardiomyopathy by decreasing peak dose levels through modification of the treatment-schedule. There are several reports showing that the reduction of peak plasma levels of anthracyclines (administered by continuous infusion) leads to a significant reduction in cardiotoxicity without decreased anti-cancer efficacy (table IV).[148-150] Torti et al.[148] reported in 1983 that doxorubicin therapy administered on a weekly schedule is associated with less anthracycline-induced cardiac toxicity than doxorubicin therapy delivered in the conventional, 3-weekly schedule. Similar results were obtained by a continuous versus rapid infusion of doxorubicin in adult paediatric cancer patients.[151,152] In contrast, Lipshultz et al.[153] reported that both, continuous and rapid infusion of doxorubicin for the treatment of children with high-risk ALL were associated with progres-

Table IV. Studies to determine the efficacy and toxicity of continuous infusion of anthracyclines

Reference	Drug	Patient no. (cancer type)	Study design	Aims	Results
Torti et al.[148]	ADR	125 (36 lymphoma; 29 breast cancer; 24 genitourinary tract cancer; 10 lung cancer; 21 sarcomas; 5 miscellaneous cancers)	Comparison	Compare ADR once every 3 weeks (n = 98) vs weekly (n = 25)	Dose of ADR (p = 0.0001) and the schedule (weekly vs 3-weekly) [p = 0.002] independently predicted the degree of endomyocardial damage in multivariate analyses; ADR administered on a weekly schedule is associated with less anthracycline-induced cardiac damage than the conventional, 3-weekly schedule
Shapira et al.[151]	ADR	62 (metastatic carcinoma of the breast or carcinoma of the ovary Stage III or IV)	Randomised, prospective study	Evaluate the possible cardiosparing effect of a prolonged infusion (6h) of ADR as compared with the standard mode of administration (30 min)	Four patients, all in the standard infusion group, developed congestive heart failure. These data suggest that slow infusion of ADR is associated with reduced cardiotoxicity
Berrak et al.[152]	ADR	97 (paediatric cancer patients)	Retrospective; compared with a control group of pts with rapid infusion	ADR CI; cardiac status was evaluated at baseline and every 6 months	Congestive heart failure: n = 1 (died of cardiac complication); significantly lower incidence of cardiotoxicity compared with a control group of paediatric patients treated with ADR with rapid infusion
Hunault-Berger et al.[154]	DNR	77 (newly diagnosed ALL)	Randomised study	Efficacy and safety of DNR CI compared with conventional 30min infusion (IV)	Similar CR-rate; higher freedom from relapse after CI (48 vs 28% at 5y; p = ns); acute toxicity (infection and infection-related death) was higher in the CI-arm; cardiotoxicity not reported
Lipshultz et al.[153]	ADR	240 (children with HR-ALL)	Randomised study	CI vs 1h infusion	Both groups showed significant abnormalities of LV structure and function; clinical cardiac manifestations and EFS did not differ; both regimens were associated with progressive subclinical cardiotoxicity

ADR = doxorubicin; **ALL** = acute lymphoblastic anaemia; **CI** = continuous infusion; **CR** = complete remissions; **DNR** = daunorubicin; **EFS** = event-free survival; **HR** = high risk; **IV** = intravenous; **ns** = not significant.

sive subclinical cardiotoxicity. In conclusion, the influence of infusion schedule on anthracycline cardiotoxicity remains a controversial issue.

3.2.2 Timed Sequential Therapy

There are several reports about efficacy and toxicity of timed sequential therapy for the treatment of acute leukaemias, whereas the benefit is still controversial (see table V). Woods et al.[155] reported that intensively timed induction therapy for patients with AML markedly improves event-free survival. In contrast, Liu Yin et al.[156] could show that standard administration of re-induction treatment in patients with refractory or relapsed AML leads to a significantly better CR rate and 3-year disease-free survival.

3.3 Risk Group Stratification

3.3.1 Minimal Residual Disease

Another option to minimise long-term adverse effects is to stratify therapy based upon the detection of minimal residual disease (MRD) during treatment. Up to now, different risk groups, receiving different intensive treatment courses, are defined by age, white blood cell count at diagnosis, chromosomal abnormality or the morphologically

determined therapy response at day 15 or prednisone-response.

In ALL, many studies have shown MRD (detected by polymerase-chain-reaction), to be an independent risk factor with regard to outcome.[159-164] Consequently, in the ongoing German ALL-BFM 2000 trial, monitoring of MRD is an important tool for treatment stratification.

Concerning AML, the monitoring of MRD is more difficult because of the greater heterogeneity of the disease. However, the PCR technique seems to be a highly sensitive method for the detection of MRD in distinct subgroups (about 20–30%) of AML patients.[15,17,165,166] The immunological monitoring of MRD by multidimensional flow-cytometry is applicable in the majority of patients treated for AML, even though this method has not been proved to be an independent prognostic factor yet.[167-169]

3.3.2 Multidrug Resistance

There are several attempts to (i) use multidrug resistance (MDR)-status to predict treatment response and (ii) develop MDR modulators for the treatment of resistant cancers. Most of these agents (e.g. verapamil, amiodarone, cyclosporin or phenothiazine) produced severe toxic effects at doses required to effectively block P-glycoprotein (P-gp) function, and modulation of P-gp in normal tissues can affect the pharmacokinetics and, thus, the toxicity of the associated chemotherapeutic agents. Recently, the third generation MDR modulator valspodar has been shown to be administered safely in combination with different cytostatic

Table V. Studies to determine the efficacy of timed sequential therapy (TST)

Reference	Patient no. (cancer type)	Study design	Treatment regimen	Results
Land et al.[157]	213 vs 215 children (B-precursor ALL)	Randomised clinical trial	12-week standard consolidation given 6 courses of intermediate-dose MTX and Ara-C vs 3-week front-loading arm as consolidation	Similar rates of adverse effects; except from CNS toxicity which was significantly higher in the front-loading arm
Liu Yin et al.[156]	170 (refractory/ relapsed AML)	Randomised clinical trial	TST vs standard application of ADE (Ara-C, DNR, VP-16) as remission re-induction treatment	CR rate, as well as 3- year DFS were significantly better in the standard ADE arm; there was no difference in haematological and non-haematological toxicity
Loeb et al.[158]	13 children (*de novo* AML)	Progress report	Experience with timed sequential induction chemotherapy consisting of daunorubicin/Ara-C/ -thioguanine (DAT) or idarubicin/Ara-C/-thioguanine (IAT)	11 children (85%) acheived CR with 'manageable toxicity'
Woods et al.[155]	295 vs 294 (AML)	Prospective randomised trial	Second induction cycle administered 10 days after the first cycle, despite low or dropping blood counts (intensive timing) vs 14 days or later from the beginning of the first cycle, depending on bone marrow status (standard timing)	Disease-free survival results at 3 years from the end of induction were superior for patients receiving intensively timed induction therapy (n = 211), 55 ± 9% versus 37 ± 9% for standard timing patients (n = 195, p = 0.0002). Most of the adverse effects in both arms were leukaemia relapse rather than drug-related toxicity

ALL = acute lymphoblastic anaemia; **AML** = acute myeloid leukaemia; **Ara-C** = cytarabine; **CR** = complete remission; **DFS** = disease-free survival; **DNR** = daunorubicin; **MTX** = methotrexate; **VP-16** = etoposide.

drugs in AML patients.[170] However, definitive results are still lacking.

Modulators of MDR might influence treatment of paediatric leukaemias. The coadministration of a modulator of e.g. P-gp activity with a chemotherapeutic agent possibly allows dose reduction of the chemotherapeutic agent. Therefore, the concentration of the chemotherapeutic agent in normal tissue is reduced, too. This might result in markedly reduced acute or long-term adverse effects.

3.4 Future Considerations

Another approach to optimise treatment might be tailoring of chemotherapy according to specific genetic subgroups with special features. Interindividual differences in drug disposition and treatment response may influence outcome in leukaemia patients. Pharmacogenomics – the determination of inherited differences in drug disposition and treatment response – is a possible approach toward individualisation of therapy with the aim to enhance efficacy and reduce toxicity of leukaemia treatment.[171] Mutations in drug metabolism enzyme genes are associated with severe toxicity in genetically predisposed patients. Mutations in the genes encoding for glutathione transferases or dihydropyrimidine dehydrogenase are associated with increased sensitivity to toxic and anti-leukaemic effects of alkylating agents, topoisomerase II inhibitors and fluorouracil, respectively.[172] Children with trisomy 21, frequently developing AML, show an increased sensitivity to chemotherapy, reflecting a pharmacogenetic predisposition.[7] Further investigation and clinical trials are needed to determine the benefit of individualised therapy based on the patient's individual genetic make-up.

4. Conclusions

The improved survival of children with malignancies has focused attention on the long term adverse effects of chemotherapy. However, a review of the literature reveals only a few reports that are based on relevant patient samples or uniquely treated groups. Most of the long-term adverse effects have not been analysed systematically. Neither incidence of long-term adverse effects nor treatment modalities, which cause specific long-term adverse effects, have been proven prospectively. The use of new diagnostic methods such as MRD monitoring, which allow optimisation of treatment, may offer clear advantages regarding the risk of severe long-term adverse effects, but most of these approaches still await prospective proof of equivalence or superiority to conventional treatment. Anthracycline-induced cardiotoxicity seems to be the best documented long-term adverse effect of chemotherapy with a direct dose dependent correlation and experimental modelling. Several attempts have been made to minimise the cardiotoxicity of anthracyclines: decreasing concentrations delivered to the myocardium by either prolonging infusion time, using liposomal formulated anthracyclines or less cardiotoxic analogues, or using cardioprotective agents. The advantage of these approaches is still controversial, but there are ongoing clinical trials to evaluate the long-term effects.[27] Other long-term adverse effects such as secondary malignancies were attributed to cytostatic treatment, but a direct association has only been proven for the administration of topoisomerase inhibitors. While all cytostatic drugs and irradiation may cause secondary malignancies, results of polychemotherapy in leukaemias further strengthen arguments proposing a direct relationship.

Most of the above presented options for minimising long-term adverse effects have resulted from theoretical models and *in vitro* studies, but only some of the modalities have been evaluated in prospective, randomised studies in patients. Although equivalent efficacy and comparable or reduced acute toxicity could be shown, long-term adverse effects are still unknown. Up to now, there has been no long-term clinical experience with cardioprotective agents, targeted chemotherapy or modulators of multidrug resistance. Thus, further efforts are necessary to optimise cancer therapy with a view to long-term adverse effects. Furthermore, long-term adverse effects following acute adverse effects such as haemorrhage, sinus vein thrombosis or infectious complications may be reduced by optimising supportive care.

All newly introduced studies should include long-term follow-up and surveillance of severe sequelae to learn more about the prevention of long-term adverse effects.

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