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Effective Childhood Cancer Treatment: The Impact of Large Scale Clinical Trials in Germany and Austria

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In Germany and Austria, more than 90% of pediatric cancer patients are enrolled into nationwide disease-specific first-line clinical trials or interim registries. Essential components are a pediatric cancer registry and centralized reference laboratories, imaging review, and tumor board assistance. The five-year overall survival rate in countries where such infrastructures are established has improved from <20% before 1950 to >80% since 1995. Today, treatment intensity is tailored to the individual patient's risk to provide the highest chances of survival while minimizing deleterious late effects. Multicenter clinical trials are internationalized and serve as platforms for further improvements by novel drugs and biologicals. Pediatr Blood Cancer 2013;60:1574–1581. © 2013 Wiley Periodicals, Inc.

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INTRODUCTION

Long-term, disease-free survival rates in children and adolescents with cancer have reached 80% under conditions permitting state-of-the-art treatment. A key to success has been the association of pediatric hematologists and oncologists in cooperative groups. Characteristic for pediatric cancer treatment in Germany and Austria is the high rate of enrolment into centralized trials of more than 90%. Consecutive clinical studies initiated by the Society of Pediatric Oncology and Hematology (GPOH) systematically assessed the value of individual drugs and their combinations and the impact and timing of local therapy in solid tumors. European collaborative trials were performed together with the International Society of Paediatric Oncology (SIOP). Clinical study groups in Germany closely collaborate with the population based "German Childhood Cancer Registry (GCCR)" which was founded in 1980 and covers over 45,000 registered cases (Fig. 1). Cases are reported nation-wide from all hospitals treating pediatric cancer patients with a data completeness of more than 95% [1], and followed up regularly for health status, including relapses or secondary malignancies. Annual reports by the GCCR summarize these epidemiological data [2].

In more recent years, countries with limited resources have started establishing effective pediatric cancer therapies. By elucidating the milestones and details of treatment development for the individual diseases and addressing current obstacles to further progress, we aim to support respective developments in less affluent areas of the world and to provide more effective cancer care to children world-wide.

Optimization of Pediatric Cancer Treatment by Clinical Studies

Motivated by the rarity of the diseases and the largely fatal outcome, pediatric oncologists in the early 1970s started to systematically collaborate. The first multicenter treatment study in Germany was initiated by Fritz Lampert (University of Gießen, Germany) for acute lymphoblastic leukemia (ALL) in response to encouraging results with a combined chemotherapy schedule pioneered by Donald Pinkel and co-workers (St. Jude Children's Research Hospital, Memphis, USA) [3,4]. Since 1970, Hansjoerg Riehm (Freie Universitaet Berlin, Germany) and his coworkers introduced a more intensive combination treatment, resulting in over 50% survival [3,5,6]. This led to the foundation of the BFM

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The authors dedicate this review to Hansjörg Riehm on the occasion of his 80th birthday.

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study group[1] in 1976 and to rapidly increasing survival rates in ALL [7]. Today, pediatric hematologists and oncologists from more than 70 hospitals in Germany, Austria, and Switzerland, and more recently also from Italy and further countries, contribute to this collaboration. Working groups for leukemias and solid tumors were established in 1966 and 1973, respectively, and fused to the GPOH in 1991. The main objective was to run population-based national and international trials to continuously improve the quality of treatment, often by applying randomized designs. Time intervals between studies are bridged by continued treatment according to the best standard of care and data collection within registries. More than 90% of children and adolescents diagnosed with cancer are enrolled in multicenter studies or interim registries by one of 25 GPOH study groups to receive disease-specific and most often risk-stratified, treatment (Table I). Uniform study treatment avoids selection bias to specific subgroups or disease stages. National registration of childhood cancer patients to a similar extent has only been reported from the Nordic Society of Pediatric Hematology and Oncology. The interaction of the GPOH with the individual study groups and the participating clinical centers is defined in detail by a body of regulations first published in 1998 and revised in 2010. An integral rule is that study group leaders are assigned by the GPOH, based on election by the board of directors and members. This aims to ensure the highest possible professional and scientific qualification.

A critical component of study groups are centralized diagnostic reference laboratories for all relevant aspects of disease classification and response, including (histo)pathology and/or cytology, immunophenotyping, molecular/cytogenetics, and minimal residual disease (MRD) quantification. The resulting data quality is a prerequisite for establishing innovative diagnostic methodologies. Central reference institutions were also defined for imaging studies, and study centers are assisted by designated specialized surgeons and radiotherapists. These logistics have allowed the development of study centers into competence centers providing highly qualified central consultations for individual cases. Survival analyses are performed in close collaboration with the GCCR. The 5-year overall survival rate among children with cancer in general has improved from $<20\%$ for patients before 1950 to $>80\%$ for those diagnosed between 1995 and 2004 (Fig. 2) [2]. To enhance the translational value of the clinical studies, experimental molecular and cellular biology studies are done in close conjunction with the clinical trials and current registries. The increasing gain of information from clinical trials is illustrated by the scientific output of AML BFM studies (Fig. S1).

Treatment Optimization in Individual Diseases

Our review focuses on Germany and Austria and on studies performed by or in close collaboration with the GPOH. Key findings in other countries will be mentioned where relevant. The development is exemplified by some relatively frequent childhood cancers, whereas others such as rhabdomyosarcomas, germ cell tumors, and Langerhans cell histiocytosis [8–10] are not described in detail.

Acute Lymphoblastic Leukemia (ALL)

The development of curative therapy for children with ALL has become a paradigm for effective clinical research in cancer. Key to success was the intensive combination of various drugs with single-agent efficacy [5,6]. Prospective randomized treatment trials performed within the BFM study group resulted in stepwise further improvements [7,11]. One insight of exceptional and international importance was that delayed re-intensification is critical for relapse-free survival in both high- and standard-risk situations [12]. Response to an initial 7-day prednisone window emerged as a significant factor predicting event-free survival (EFS). The concept of stratification of treatment by risk adjustment was first introduced in the 1979 study [13]. In the 1990s, efforts to reduce potential late effects of therapy gained importance. While cranial radiotherapy was effective to prevent CNS relapse [14], it was also responsible for secondary CNS malignancies and neurocognitive late effects. ALL-BFM results showed that cranial irradiation could be dose-reduced in high risk subtypes and in T-ALL and safely replaced by intrathecal and high-dose systemic methotrexate in all others [15]. Molecular quantification of MRD in remission marrow has emerged as an effective tool to predict relapse and modulate treatment intensity [16]. Survival rates have now reached 90% (Fig. 3). The current BFM study (AIEOP-BFM ALL 2009, Table I) is an international collaboration including six further countries besides Germany. In the 1980s, the CoALL study group started performing a number of consecutive trials in childhood ALL which achieved overlapping results with an alternative design [17]. Relapse of ALL in children in Germany and Austria is exclusively treated within the ALL-REZ BFM study that has prospectively evolved alongside the ALL-BFM study since 1983. Moreover, since 2003, hematopoietic stem cell transplantation (HSCT) in ALL is performed within the prospective, international, multicenter trial ALL-SCT BFM with the goal to ensure the highest standard of care and optimize transplantation [18].

Acute Myeloid Leukemia (AML)

The first cooperative treatment study for childhood AML in Germany was initiated in 1978 [19]. Cytosine arabinoside and anthracyclines were combined in highly intensive induction and consolidation elements, followed by maintenance therapy and preventive cranial irradiation. The 5-year survival rate increased from $<10\%$ to 42%. Five subsequent trials have further increased survival to now 70% [20–22], and even 90% in the subgroup of core-binding factor leukemias [23]. Besides step-wise improvements of the combinatorial treatment design and refined clinical and molecular risk stratification, the advent of allogeneic HSCT has added benefit in children with the highest risks of relapse and in second remission [24,25]. Importantly, progress has critically relied on improvements of emergency strategies to avoid early deaths by hemorrhage, and on advances in infectious disease management along with an increased awareness of life-threatening complications [26]. Assessment of the value of cranial irradiation in the 1980s indicated a lower relapse rate in irradiated patients [27]. Dose reduction from 18 to 12 Gy did not convey an increase in relapse rates [28]. Recently, cranial irradiation was replaced by intensified intrathecal therapy in CNS-negative patients. As in ALL, additional studies addressing the management of patients with relapse and HSCT have started in 2001 and 2010, respectively. Studies in Myelodysplastic Syndromes (MDS) have been performed since 1998 within the framework of the European Working Group of MDS and JMML in Childhood (EWOG-MDS) [29].

[1]Berlin, Frankfurt, Muenster study group, founded by Hansjoerg Riehm, Bernhard Kornhuber, and Guenther Schellong.

TABLE I. GPOH Study Groups and Treatment Trials (T) or Registries (R) in Germany (2012)*,**

Diagnosis	Study groups	Title of trial/register	Comments	
Acute lymphoblastic leukemia	ALL-BFM	AIEOP-BFM ALL 2009	Primary ALL	T
		ALL-REZ BFM 2002	Relapse	R
		ALL-SCT BFM 2003	Stem cell transplantation	R
		EsPhALL	Ph+ ALL	T
		Interfant 06	ALL in infants	T
	CoALL	CoALL-08-09	Primary ALL	
Acute myelogenous leukemia	AML-BFM	AML-BFM-2004	Primary AML	R
		AML Relapsed 2009	Relapse	R
		AML-SCT BFM 2007	Stem cell transplantation	T
		ML-DS 2006	Down syndrome	R
		TMD Prävention 2007	Down syndrome	T
Chronic myelogenous leukemia	CML-paed	CML-paed II		T
CNS tumors	HIT	HIT 2000	PNET/medulloblastoma, ependymoma	R
		HIT-HGG-2007	High grade gliomas	T
		HIT-REZ-2005	Relapsed PNET/medulloblastoma, ependymoma	T
	Craniopharyngeoma	Kraniopharyngeom 2007	Craniopharyngeomas	T
	SIOP-LGG	SIOP-LGG-2004	Low grade gliomas	R
	CPT-SIOP	CPT-SIOP Registry	Choroid plexus tumors	R
	Germ cell tumors	SIOP-CNS-GCT II	CNS germ cell tumors	T
Ewing sarcoma	Ewing	Ewing 2008		T
Hepatoblastoma	GPOH Liver tumor	GPOH Liver tumor registry		R
Germ cell tumors	Germ cell tumors	MAHO 98		R
		MAKEI 96		R
Hemophagocytic lymphohistiocytosis	HLH	HLH 2004		T
Hodgkin lymphoma	EuroNet-PHL	EuroNet-PHL-C1		T
		EuroNet-PHL-LP1		T
Langerhans cell histiocytosis	LCH	LCH III		T
Myelodysplastic syndromes	EWOG MDS	EWOG MDS 2006	Standardization of diagnosis	T
Nephroblastoma	SIOP/GPOH	SIOP 2001/GPOH		T
Neuroblastoma	NB	NB 2004/NB 2004-HR		T
Non-Hodgkin-lymphoma	NHL-BFM	NHL-BFM Registry 2012		R
		ALCL-Relapse	Relapse	T
Osteosarcoma	EURAMOS	EURAMOS-1		T
Rhabdoid tumors	EU-RHAB	EU-RHAB		T
Soft tissue sarcoma	CWS	CWS-SoTiSaR		R
		CWS-Guidance	Treatment recommendation	R
		CWS-2007 HR		T
Nasopharyngeal carcinoma	NPC-GPOH	NPC-2003-GPOH		T
Malignant endocrine tumors	GPOH-MET	GPOH-MET registry	Thyroid cancer, tumors of suprarenal gland, pheochromocytoma, gastroenteropancreatic endocrine neoplasias	R
Rare tumors	Rare tumors	STEP		R

*Source: http://www.kinderkrebsinfo.de/e1676/e9032/e1758/index_eng.html; **One hallmark of GPOH studies is that individual study groups for each disease perform the clinical trials, with nation-wide patient accrual throughout Germany and Austria. GPOH registries bridge intervals between clinical studies. Registries provide detailed treatment recommendations, including supportive care, according to the best standard of care. While clearly inferior to clinical trials in gaining knowledge, registries aim to comprehensively document clinical information under continuing uniform treatment and to systematically perform accompanying translational research. Over 90% of pediatric cancer patients are reported to GPOH clinical trials and interim registries [1,2].

Non-Hodgkin-Lymphoma (NHL)

In the first BFM studies, NHL was treated uniformly in close adaptation to the protocols developed for childhood ALL [30]. Major improvement was achieved when biological and pathogenetic differences of NHL-subtypes led to the definition of three treatment groups (TG1–3): ALL-type treatment was effective in B and T precursor cell lymphomas (TG1), with a cure rate of 80–90% [31,32], whereas children with disseminated mature B-NHL only had a 34% chance of EFS [30]. Therefore, a qualitatively different regimen was designed for these patients (TG2). Taking into account the extremely high proliferation rate of these lymphomas, treatment was intensified early, with continuous high cytotoxic drug exposure. This strategy was effective, increasing EFS to 67% in disseminated disease, and almost all patients with localized B-NHL were cured [33]. Intensive intrathecal therapy was found to prevent CNS relapse in >99% of children without initial CNS involvment.

Subsequent efforts focused on tailoring treatment intensity to the individual risk of relapse [34,35]. Attempts to minimize intensity of the highly aggressive therapies require caution since the chances of

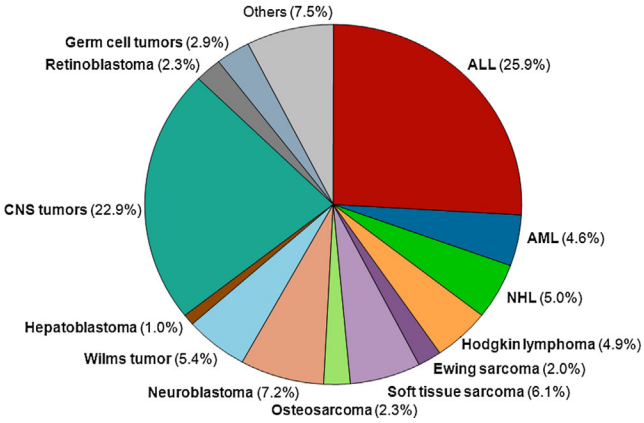

Fig. 1. Relative frequency of patients under 15 in Germany registered between 2000 and 2009 according to the most frequent diagnoses [2].

efficient salvage after failure of first-line therapy remain poor despite intensive re-induction and introduction of HSCT [36]. As one of the first targeted strategies in a childhood cancer, rituximab was found active as a single-agent in pediatric B-NHL [37]. Its role in this disease is the subject of current study concepts both in North America and Europe. For the third treatment group (TG-3), anaplastic large cell lymphoma (ALCL), both ALL-type and B-NHL-like treatment resulted in EFS rates of 70–75% [38–40]. Different from other NHL subtypes, patients with relapsed ALCL have a significant second chance to survive with low-dose long term maintenance therapy or by allogeneic HSCT, leading to overall survival rates of 90% [41].

Hodgkin Lymphoma

Hodgkin lymphoma was the first cancer in which the focus of attention shifted from survival alone to the reduction of late effects of therapy. Combined modality treatment with radio- and chemotherapy resulted in a rapid increase of EFS rates to over 90% in the mid-eighties. The central objective of subsequent consecutive multicenter studies was to identify effective therapy concepts with minimal long-term toxicity. From 1982, patients in Germany and Austria were risk-stratified according to disease stage [42]. The common practice of explorative laparotomy and splenectomy of early studies was omitted [43]. At the same time, extended-field irradiation was safely replaced by modified involved-field/involved node irradiation. The high survival rates were maintained with step-wise dose reductions of radiotherapy in subsequent studies [43,44]. Longitudinal follow-up data have now confirmed the concerns regarding relevant late effects. High rates of endocrine dysfunction, heart disease, and secondary solid tumors were observed among survivors and were clearly associated with radiotherapy [45–47]. First attempts to eliminate procarbazine to avoid testicular dysfunction and infertility resulted in a marked reduction of outcome [48]. Later, procarbazine was safely substituted by etoposide in the two induction cycles [44]. Study HD-2002 demonstrated comparable effectiveness of procarbazine-free and procarbazine-containing regimens in boys and girls, respectively, with survival and EFS rates at 5 years of 97 and 89% [49]. In 2005, the GPOH group opened to the European Network on Pediatric Hodgkin Lymphoma group. The first pan-European study (EuroNet-PHL, Table I) starting in 2007 introduced response evaluation by functional imaging to allow for individual adaptation of treatment intensity. Radiotherapy is completely omitted in patients with negative positron emission tomography scans after induction.

Ewing Sarcoma

Systematic development of Ewing sarcoma therapy in Germany started in 1981 [50]. Treatment was derived from the T9 protocol initiated by Gerald Rosen (Memorial Sloan-Kettering Cancer Center, NY) with the most promising results to that date [51]. In 1992, a first "European Intergroup Cooperative Ewing's Sarcoma Study (EICESS)" was initiated by Alan Craft (Newcastle University, UK) and Heribert Juergens (University of Muenster,

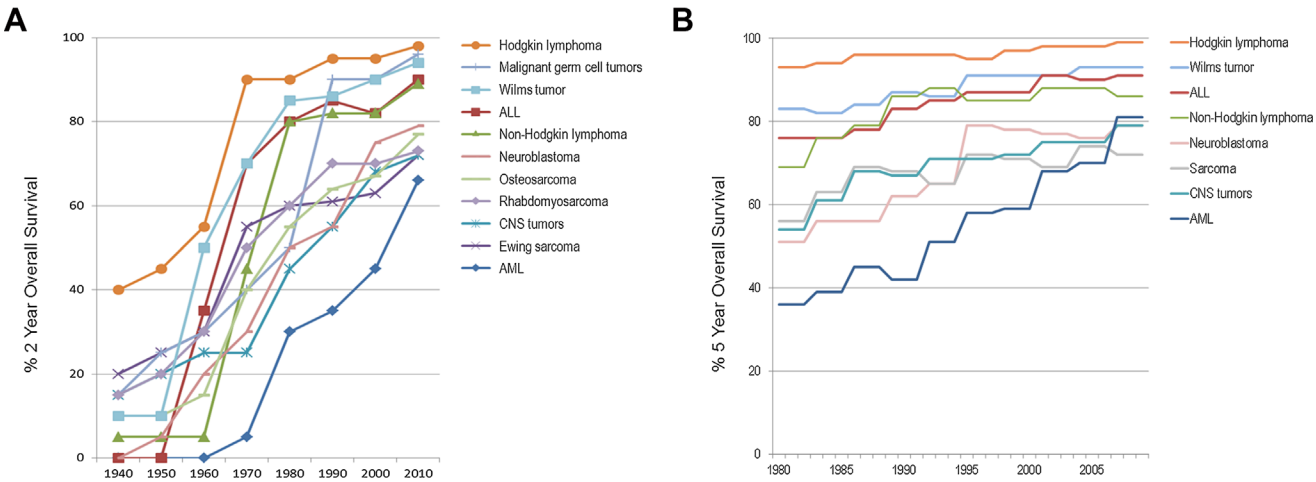

Fig. 2. Improvement of cancer survival rates in children in Germany. **A**: 2-year overall survival between 1940 and 2010. The reason for showing 2-year survival rates is the fact that follow-up was not longer than 2 years prior to 1970.Source: Kompetenznetzwerk Pädiatrische Hämatologie und Onkologie (KPOH). Adapted from http://www.kinderkrebsinfo.de/health_professionals/general_information/index_eng.html by D. Reinhardt. **B**: 5 year overall survival by year of diagnosis in 3-year-groups. Data source: German Childhood Cancer Registry.

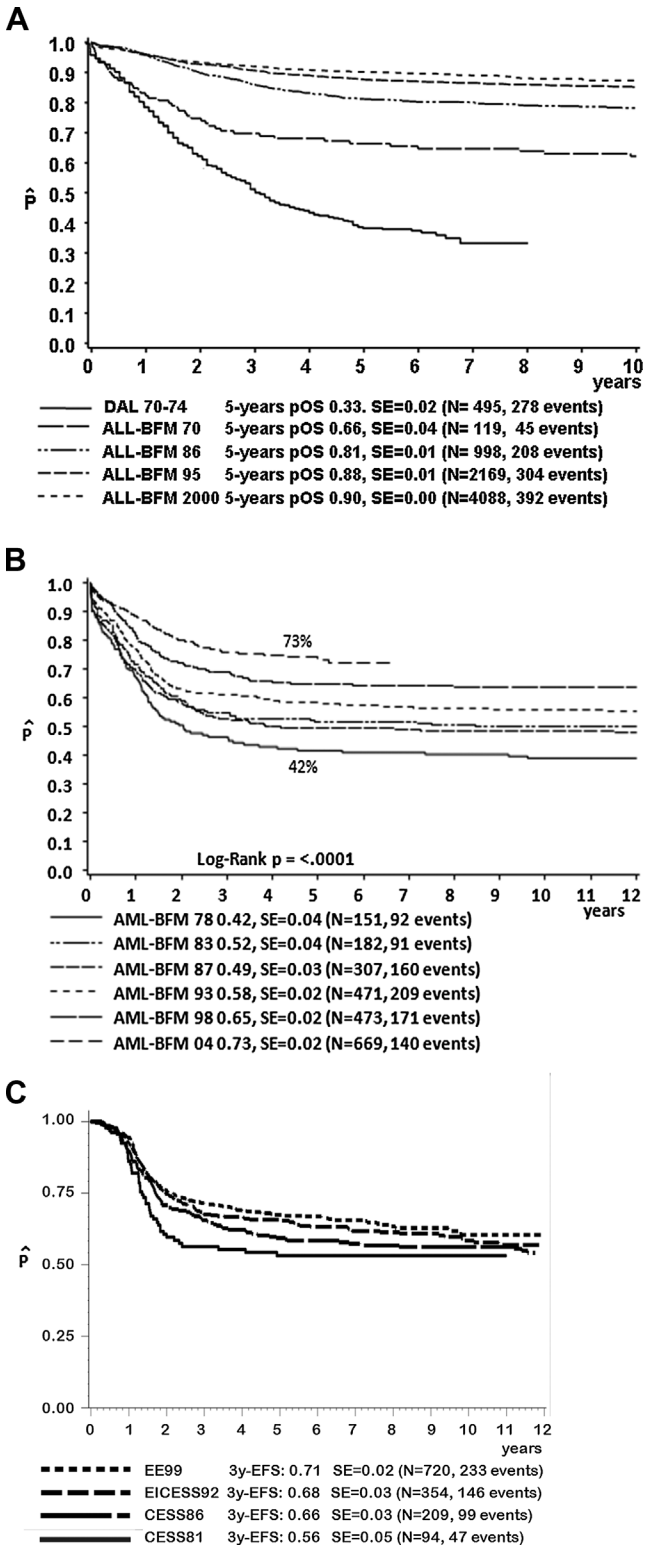

Fig. 3. Improvement of 5-year overall survival rates in ALL-BFM studies (**A**) and AML-BFM studies [22] (**B**), and of 3-year event-free survival rates in Ewing sarcoma studies (**C**) since 1970.

Germany). The treatment strategy included neoadjuvant multi-drug chemotherapy, surgery, and/or radiotherapy. Randomized study questions included the comparison of ifosfamide and cyclophosphamide and introduction of etoposide. Both high intensity of chemotherapy and local therapy were found essential for outcome [52,53]. Even patients with disseminated disease at diagnosis benefit from local therapy [54]. Radiotherapy for Ewing sarcoma is active and valuable, but compared to surgical tumor removal, irradiation alone bears a higher risk of local recurrences.

The European Ewing Sarcoma Study Group trials since 1999 have stratified patients into three risk groups according to tumor size, response to chemotherapy, and pulmonary metastases and/or overt dissemination. Current 3-year EFS rates are between 25% and 30% in patients with skeletal metastases and 75–80% in patients with localized disease and good response to chemotherapy. Subject of the current trial is the value of add-on non-cytostatic drugs (zoledronic acid) and randomized evaluation of high-dose therapy with autologous stem cell rescue in high-risk disease.

Osteosarcoma

In osteosarcoma, surgery alone cures less than 20% of patients. Neoadjuvant chemotherapy prevents dissemination, controls micrometastases, and partially devitalizes the tumor [55]. The interdisciplinary cooperative German–Austrian–Swiss osteosarcoma study group COSS, founded by Kurt Winkler (University of Hamburg, Germany), started performing multicenter clinical studies in 1977. The application of neoadjuvant therapy was introduced with the second study, which also established associations of smaller tumor size and favorable histological response to chemotherapy with increased relapse-free survival [56]. Optimal local therapy consists of resection of all detectable tumor sites with adequate margins, including pulmonary metastases. Along with the availability of endoprosthetic devices, surgical techniques have evolved to allow limb-salvage surgery with adequate surgical margins in increasing numbers of patients [56]. The optimal surgical approach remains an individual decision, taking into account tumor localization, anatomy, and age. Despite the relative radioresistance of osteosarcoma, radiotherapy may have a role in situations where surgical margins are limited by tumor localization [57]. EFS after 10 years increased to the current 66% in COSS-86 [58]. In 2005, the study group was further internationalized to initiate the EURAMOS-1 study [59]. Study questions are the role of immune modulation by α-interferon maintenance in histologic good responders and of intensive salvage chemotherapy in poor responders.

Neuroblastoma

The first cooperative German Neuroblastoma trial was initiated in 1979 when survival rates in patients with disseminated disease (stage 4) were still dismal [60]. Intensive chemotherapy combinations induced remissions in the majority of stage 4 patients, and the 5-year EFS increased from 1% (NB79) to 33% (NB97) [61]. Unfortunately, treatment intensification was accompanied by an unacceptable therapy-related death rate [62]. In a parallel effort within the European Neuroblastoma Research Network, randomized comparison demonstrated a significant reduction of febrile neutropenic episodes by prophylactic granulocyte-colony stimulating factor [63]. Another problem was the occurrence of secondary

leukemias, attributed to prolonged exposure to oral etoposide, which led to modifications of maintenance chemotherapy [62,64]. Following first controlled trials showing a benefit of autologous transplants in stage 4 disease [65,66], prospective randomized comparison within the GPOH trial NB97 confirmed the superiority of myeloablative over maintenance therapy [67].

While neuroblastoma screening at 1 year of age by catecholamine metabolites in urine failed to decrease mortality [68], further progress has relied on adjustments of treatment intensity according to age, stage, and genetic risk factors [69]. Trials NB95-S and NB97 demonstrated that chemotherapy can be omitted in infants with localized tumors or asymptomatic stage 4S disease unless MYCN is amplified [70]. The current protocol NB2004 has extended the watch-and-wait strategy so that today 57% of patients with localized, even unresectable neuroblastomas can be spared chemotherapy without hampering the overall survival rate of 98%. Current efforts aim to improve risk stratification by molecular tools [71,72] and to increase the outcome in high-risk patients that has remained unsatisfactory despite myeloablative chemotherapy, (131)I-MIBG therapy and differentiation-inducing maintenance therapy. Immunotherapy with a monoclonal antibody against the neuroblastoma-associated antigen G_{D2} has failed to demonstrate a clear positive impact on outcome within GPOH studies [73]. In a more recent study in North America, anti-G_{D2} antibody combined with granulocyte-macrophage colony-stimulating factor and interleukin-2 was associated with a significantly improved outcome over standard therapy in high-risk neuroblastoma [74]. The addition of cytokines may have augmented G_{D2} antibody-dependent cell-mediated cytotoxicity and thus explain the contrasting results of the two studies. Current efforts aim to develop more effective G_{D2}-antibody based combination therapies in neuroblastoma.

Wilms Tumor

Current Wilms tumor treatment in Europe is stratified according to age, histological subtype and disease stage, and relies on preoperative chemotherapy, radical surgical tumor resection, generally by tumornephrectomy, and post-surgery chemotherapy in the majority of patients. This highly successful strategy has emerged from a series of multicenter clinical trials both in Europe and North America. The SIOP studies from 1971 to 1976 addressed the value of preoperative radiotherapy, later replaced by chemotherapy, to reduce tumor volume, eliminate micrometastases, and allow stratification according to histological response [75–77]. In Germany, the GPO(H) Wilms Tumor Group, initially led by Peter Gutjahr (University of Mainz), started to systematically treat patients in 1976 [78,79]. To extend randomized trials to larger cohorts, the German society joined the SIOP trials in 1989. Opposed to immediate surgery, as favored in North America, the risk of tumor rupture is significantly lower after preoperative therapy. A 4-week cycle with vincristine and actinomycin is generally well tolerated and has become standard of care for localized tumors in Europe [80,81]. Local radiotherapy was reduced to few indications (intermediate risk histology and stage III, high risk histology and stage II or III with the exception of blastemal subtype, and stage IV and V dependent on the local stage) affecting around 20% of children. With the high EFS of now 89% in localized stages, further studies aimed to reduce toxicity, treatment burden and potential late effects without loss of effectiveness. These efforts have focused on the adjustment of postoperative chemotherapy to individual risk groups. In the randomized study SIOP-93, post-surgery treatment could be safely reduced to only 4 weeks in stage 1 disease with intermediate risk histology, including more than half of the patients [82]. Treatment as high-risk disease is now recommended for patients with blastemal type histology [83]. The most recent trial, SIOP 2001, has focused on treatment-associated morbidity and late cardiac toxicity in patients with higher disease stages [84]. Future studies aim to optimize tailoring of treatment by including molecular characteristics of the disease.

Medulloblastoma

Medulloblastoma is discussed as one example of pediatric central nervous system (CNS) tumors. An important step in medulloblastoma treatment was introduction of systemic chemotherapy [85,86]. The aims of the national brain tumor ("Hirntumor", HIT) studies, initiated by the GPOH in 1988, were to increase survival rates as well as the quality of life of survivors. Neoadjuvant chemotherapy following surgical removal and prior to radiotherapy was effective to reduce the high risk of relapse in young children with large and incompletely resected tumors and increased survival to over 60% [87,88]. In patients with non-metastatic disease, postoperative radiotherapy followed by maintenance chemotherapy led to excellent overall survival rates of 91% after 10 years [88]. To avoid the cognitive deficits resulting from radiotherapy in young children, intensive postoperative chemotherapy alone was evaluated and found to induce prolonged remissions and avert or defer radiotherapy in most patients [89]. The multicenter trial HIT 2000 has further individualized therapy. Age at diagnosis and metastatic stage of disease are important stratification criteria. Histologic subtypes as well as molecular parameters were shown to be of epidemiological, clinical, and prognostic relevance [90]. Future studies will focus on validation of these findings aiming to adjust therapy to the distinct molecular subgroups. The recent HIT-SIOP-PNET4 study [91], a European collaboration, has provided the basis for a first prospective trial for childhood brain tumors that will include biological criteria for risk-adapted stratification of treatment.

Challenges

Although major advances can no longer be expected from the classical treatment modalities alone, efforts to further improve the chemotherapeutic backbones of standard and high risk therapy are ongoing. These optimization studies are now facing substantial problems in planning and conduct. As a consequence of the increased EFS, high numbers of patients need to be treated to obtain statistically significant information regarding superiority or noninferiority of experimental regimens. To avoid unacceptably long recruitment periods, childhood cancer trials are more and more internationalized. One example is the future trial for relapsed ALL that will recruit patients from 19 countries over three continents.

An important barrier for further progress are the increasing regulatory requirements. In 2004, the German Drug Law was amended to conform to the European directive 2001/20/EG that regulates implementation of good clinical practice in clinical trials. Non-commercial treatment optimization trials now have to comply with the same regulatory requirements as industry-initiated drug development studies that aim to bring a new compound to the

market. The resulting increase of the regulatory and administrative complexity has amplified the cost, which can no longer be covered by non-profit organisations and donations. Qualified staff and professional structures that meet the specific requirements of the law have been established, but funding and bureaucracy issues remain unresolved. As a consequence, many current clinical trials are prolonged or continued as registries with only limited gain of information (Table I).

Improved survival in high-risk subgroups of individual cancers will rely on novel treatment modalities that act by fundamentally different mechanisms than standard chemotherapy. The emergence of next-generation sequencing technologies allows detailed insights into the cancer genome and the signaling pathways that drive malignant growth [92–94], and new classes of oncology drugs are under development that target cancer-associated molecular aberrations [95].

A considerable challenge is translation of expanding knowledge into novel treatment strategies. The number of early clinical trials in pediatric malignancies is low, despite new European regulations aiming to advance pediatric anticancer drug development by mandatory pediatric investigation plans for the marketing authorization of new products (discussed in [96]). International cooperative networks have now started to systematically establish new drug development strategies for pediatric malignancies together with national academic groups. In Europe, the Innovative Therapies for Children with Cancer (ITCC) Consortium was launched to structure academic pediatric drug development in cooperation with regulatory bodies and pharmaceutical enterprises. Following up on the central insight gained from the early stages of pediatric cancer treatment more than 40 years ago, effective combinations of novel drugs and therapies will have to be discovered.

Besides the need for novel therapeutics, a central issue in pediatric oncology is the high toxicity of current therapies. Although the majority of individuals have a normal life after cancer treatment, substantial late effects have also been observed, including a risk for secondary malignancies [97]. Long-term surveillance of the increasing number of childhood cancer survivors to prevent avoidable health risks is an important task within and beyond pediatric oncology. Comprehensive registries for late effects and studies of the quality of survival are indispensable [98]. The challenge remains to translate these observations into less toxic therapies without compromising efficacy.

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We sincerely apologize to all those who we have not cited in this review due to limits of space. We did not mean to undervalue further seminal work by the selection made here and refer to more specific reviews.

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