



## Therapy concepts in the context of precision medicine for pediatric malignancies – children are not adults

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**Summary** Cancer remains the leading cause of death from disease among children beyond the age of one. Survival of pediatric patients with cancer has dramatically improved over the last decades but some tumors remain almost intractable and relapse is still associated with an infaust prognosis. Despite the heterogeneity of pediatric malignancies, most treatments include the same set of generic therapies. Optimizing delivery of conventional therapeutics has been the driving force behind continuous improvements but further escalation of conventional therapy is unlikely to improve outcomes. The limited success of targeted drugs in pediatric cancer patients, originally developed for cancers in adults, can be connected to the different etiology of tumors in children versus adults. In addition, many pediatric cancers lack reliable biomarkers, cannot be studied in large cohorts and only few available therapies target aberrations specific for certain pediatric cancers.

These observations have led to the establishment of pediatric precision-medicine programs. The major goal of these programs is to identify patient-tailored molecular treatment plans that will eventually improve quality of life and survival. Despite the initial euphemism, the impact of actionable matched treatments and the most adequate value-based genomics strategies are not yet well established. A non-competitive collaborative model based on pediatric cancer priorities and strong collaboration between academia, pharmaceutical companies and regulators is needed. In the near future, clinical trials need

to focus on biologically defined patient subsets, in an even smaller patient population. A major collaborative effort between all associated groups will be necessary to ensure success of pediatric precision cancer medicine.

**Keywords** Pediatric oncology · High throughput genomic profiling · Collaborative innovative trial design

Despite major progress over the last 50 years cancer remains the leading cause of death from disease among children beyond the age of one with approximately 2.5 newly diagnosed patients per 100,000 individuals [1]. Due to both cooperative protocols and multidisciplinary treatment, overall survival of pediatric cancer patients increased dramatically. Up to the early 1970s, the 10-year survival rate of patients younger than 20 years was below 20%. Today, 83% of these patients are alive 10 years after initial diagnosis. This overall success story of pediatric oncology is largely due to excellent outcomes in the treatment of more common cancers [2]. The rate of progress has been greater in hematologic malignancies, neuroblastoma, gonadal cancers, and some central nervous system tumors than in other solid tumors, where outcomes have almost plateaued over the last decade [3]. Still, several childhood solid tumors remain intractable—especially metastatic disease is hard to treat and is associated with a poor outcome [4]. In addition, 20% of pediatric cancer patients relapse (corresponding to 400 patients/year in Germany or 40/year in Austria) and of those only about 10% can be cured [2, 5].

Despite the complexity and variability of pediatric cancers, most are treated with the same set of generic therapies: surgery, radiation therapy, chemotherapy,

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and immunotherapy [6]. Optimizing delivery of conventional therapeutics has been the driving force behind continuous improvements in pediatric cancer survival over the last 40 years. However, further escalation of conventional therapy is unlikely to yield improvement in cancers that currently have unacceptably low cure rates or patients with relapsed or primary metastatic disease [6]. In the current era where an unprecedented number of targeted and immuno-oncology drugs have been developed for adult cancers [7, 8], high hopes have been placed also in pediatric oncology as a mean to bridge that gap. However, comparably few successful examples have been directly implemented into frontline childhood cancer care: rituximab for Burkitt lymphoma, blinatumomab for acute lymphoblastic leukemia, imatinib for chronic myeloid leukemia, sorafenib for FLT3-mutated acute myeloid leukemia, dinutuximab and anaplastic lymphoma kinase (ALK) inhibitors for high-risk neuroblastoma and others. The limited success can be connected to the absence of reliable biomarkers, the lack of large cohorts, limited longitudinal studies, and the few available targeted therapies specific for children with cancer.

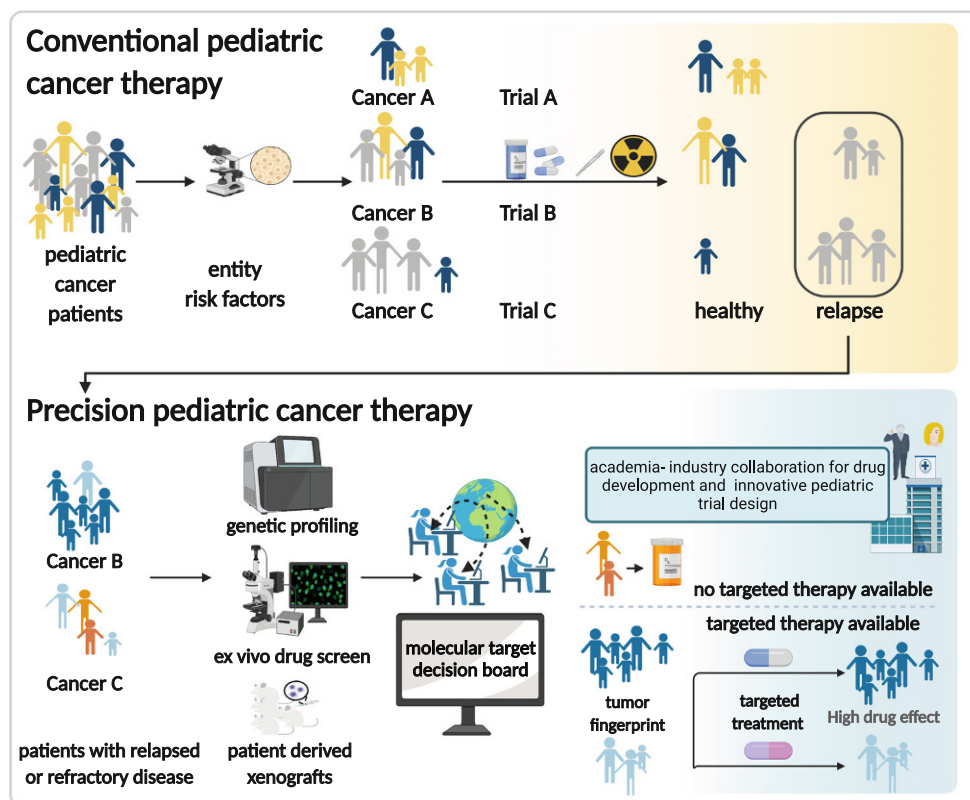
As opposed to the predominance of epithelial origin in adult tumors, pediatric cancers are diverse in their origin and are now considered as diseases of dysregulated development [9]. Revolutionary advances in next-generation sequencing technology [10–12] together with progress in chromatin and stem cell biology [13] have piloted in a new molecular understanding of childhood cancer. Evidence from mouse models of childhood cancer suggest malignant transformation in stem or progenitor cells during developmental time windows, rather than numerous mutational “hits” as frequently observed in adult cancers [14–19]. Fusion genes are more common in pediatric than in adult cancers, and certain mutations found are almost exclusive to pediatric tumors indicative of potentially novel oncogenic pathways [11, 20, 21].

These observations have prompted regulatory initiatives in Europe (The European Pediatric Medicine Regulation, 2006) and the US (Best Pharmaceutical Act, 2002; Pediatric Research Equity Act, 2003) to promote pediatric precision-medicine programs. Personalized cancer therapy is not a new concept, particularly in pediatric oncology. Established pediatric protocols already stratify patients into different risk groups according to therapy response, age and gender, disease localization, biomarkers and many other factors [22]. However, in contrast to conventional chemotherapy, which destroys both tumor and normal cells, precision medicine aims at uncovering and specifically targeting the molecular alteration of the malignancy [23]. Over the last few years several national and international programs such as MAPPYACTS [24], INFORM [25], ZERO [26], PROFYLE [27] and the TARGET [28] initiative have evolved. The unifying concept of these programs is to biologically

characterize tumor samples especially for patients with relapsed or refractory high-risk disease for which no standard of care therapy is available. State-of-the-art next-generation sequencing technologies are used to define a “fingerprint” of each individual tumor. In an interdisciplinary panel experienced pediatric oncologists, bioinformaticians, biologists, and pharmacologists classify and weigh the identified aberrations/targets found for each single patient according to clinical relevance and available targeted therapies (Figure 1). The major goal of these programs is to identify patient-tailored molecular treatment plans that will eventually improve quality of life and survival.

However, despite the initial euphemism, the feasibility of large-scale clinical use of precision medicine, the impact of actionable matched treatments and the most adequate value-based genomics strategies are not yet well established [29]. It is key to inform parents and patients upfront about relatively low rates of sustained clinical responses and potential limitations of targeted therapies due to still not yet fully recognized and predictable side effects. Furthermore, difficulties in interpreting sequencing results and their consequences for bedside medicine remain an important issue. Often, in depth tumor characterization reveals mechanistic differences in conventional entities, generates more heterogeneity and makes rare diseases even rarer. Due to their inherent pre- and post-analytical complexity interpretation and validation of precision oncology studies is especially challenging, as epidemiological and genetic variability between populations, individual tumor heterogeneities, sequencing techniques, genomic panels covered, and bioinformatics analysis differ widely between the trials and commercially available platforms [30]. First reports of three independent pediatric precision cancer medicine programs showed limited potential of genomics alone to guide selection of targeted therapies: The PEDS-MIONCOSEQ [31] and INFORM [32] studies demonstrate that a small set of patients ( $n=9$  [10%] and 2 [4%], respectively) had a clinical response following initiation of a targeted therapy. In the iCat [33] study, which included over 100 patients, the 3 patients who received a targeted therapy failed to show objective responses. However, later, larger studies could identify subgroups benefitting from molecularly matched targeted treatment (Tilburg, abstract ASCO 2021 [25]). To increase the predictive value, most of these programs now include drug sensitivity and resistance profiling (DSRP) on either patient cells or patient-derived xenografts. In combination with genomic profiling, DSRP can generate a more comprehensive understanding of the tumor, allowing appropriate therapy selection for each individual patient [34].

Consequently, pediatric cancer is to be treated in a more individualized way and clinical trials need to focus on biologically defined patient subsets, in an



**Fig. 1** Graphical display of conventional versus precision cancer therapy for refractory and relapsed pediatric patients. Conventional chemotherapy (*top*) relies on entity specific treatments derived from a combination of histopathology and biomarkers. Patients are treated according to standardized international protocols, which mainly include a combination of chemotherapy, radiation, surgery, and immune/targeted therapy for selected cases. Precision cancer therapy (*bottom*) uses genomic profiling (genome, exome, RNA, and methylation sequencing) of tissue from each individual cancer patient in combination with experimental data on patient derived tumor cells using xenograft models or ex vivo drug testing. Gen-

erated data is discussed in a multidisciplinary molecular tumor board, a targeted treatment plan including potential biomarkers for response evaluation are selected for every patient. The patient is enrolled in a clinical study. For patient groups where no targeted therapy is available a collaboration with industry for drug development or pediatric clinical trial design is initiated. At present, precision medicine options are mainly available for refractory and relapsed (R&R) patients but the goal is to offer precision medicine approaches to all patients also during first-line therapy. This figure was created with BioRender.com and is not included under the Creative Commons CC BY license of this publication

even smaller patient population. National and international collaborative studies are therefore required to attain sufficient patients and complete trials in a timely manner. The key challenge is to design trials that can clearly delineate the effect of the new agent under study. Innovative adaptive study design is needed, based on the underlying cancer biology rather than certain cancer types [35]. Furthermore, new endpoints that utilize functional imaging or molecular biomarkers should be incorporated into clinical trials as a measure of response and MRD. To achieve this ambitious goal, cooperation with regulatory bodies, pharmaceutical enterprises, parents, and patients is key. However, childhood cancer is considered a rare disease and the market for pediatric cancer treatments is small. In addition, several non-commercial barriers have also been highlighted as possible blocks to drug development in childhood cancer: rare populations leading to slow accrual and small samples sizes for conventional trial designs,

the need for suitable pediatric formulations (tablets and capsules are less appropriate than intravenous or liquid formulations), concerns for both acute and long-term safety in the developing child and anxiety over real and perceived ethical difficulties in studying new agents in this vulnerable population [36]. In addition, there is a smaller number of druggable genetic aberrations in childhood cancers and pharmacokinetics/dynamics differ significantly between infants, adolescents, and young adults. In this system drugs that are potentially of great interest in pediatrics, but without an adult indication are not likely to be tested in pediatric clinical trials. This is of particular concern since the pathogenesis of pediatric cancer is largely different from adult cancer, as stated above.

To overcome this issue a non-competitive collaborative model based on pediatric cancer priorities and strong collaboration between academia, pharmaceutical companies and regulators is needed. In this scenario the pediatric oncology academic community

performs preclinical testing and selects the strongest candidates for clinical trials together with pharmaceutical companies and regulators. This would allow promising novel therapies to be studied in parallel and sequentially using innovative biomarker-led trial designs, (e.g., multi-arm Bayesian adaptive designs) to allow for more feasible, efficient, and expedited clinical trials [37]. The Innovative Therapies for Children with Cancer (ITCC) Consortium [38] is an example of such an institution. The ITCC is a non-profit organization and gathers 63 European pediatric oncology departments with expertise in conducting early phase trials in children and adolescents, and 25 European research laboratories. The aim of this organization is to develop novel therapies for the treatment of pediatric and adolescent cancers in cooperation with regulatory bodies, pharmaceutical enterprises, parents, and patients. Since its foundation in 2003 the ITCC has paved the way for advancing pediatric cancer therapy.

As we continue into the 21st century, our increased understanding of the molecular and genetic basis of childhood cancer will facilitate further refinement of risk-adapted therapy that utilizes molecular and genetic signatures for risk stratification. A major collaborative effort between all associated groups—clinicians, scientists, insurers, biopharmaceutical companies, regulators, and patients—will be necessary to keep driving pediatric precision cancer medicine forward and make it a viable field that benefits all [39].

### Take home message

- Childhood cancers are biologically different from adult cancer entities and need different therapy concepts.
- A major collaborative effort between all stakeholders is needed.

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