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The Promise and the Reality of Genomics to Guide Precision Medicine in Pediatric Oncology: The Decade Ahead

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Abstract

Much has been written about the promise of "precision medicine", especially in oncology, where somatic mutations can influence the response of cancer cells to "targeted therapy". There have been successful examples of targeted therapy improving the outcome of some childhood cancers, such as the addition of an ABL class tyrosine kinase inhibitor to conventional chemotherapy substantially improving the cure rate for patients with BCR-ABL1 positive acute lymphoblastic leukemia. Although there are other mutations serving as putative targets in various childhood leukemias and solid tumors, effective targeted therapy has yet to be established for them in prospective clinical trials. There are also uncertainties about which "targeted therapy" to use when patients have multiple targetable genomic lesions in their cancer cells, given the paucity of data upon which to develop evidence-based guidelines for selecting and integrating targeted agents for individual patients. There are also multiple examples of inherited germline variants for which evidence-based guidelines have been developed by CPIC to guide the selection and dosing of medications in children with cancer. Clinical pharmacology is poised to play a critical role in both the discovery and development of new targeted anticancer agents and their evidence-based translation into better treatment for children with cancer. To embrace these challenges and opportunities of "precision medicine", clinical and basic pharmacologists must expand the depth of our science and the bandwidth of our translational capacity, if we are to optimize precision medicine and advance the treatment of cancer in children and adults.

Introduction

Cure rates for most childhood cancers have improved impressively over the last several decades, with the collective cure rate increasing from about 20% in the 1960s to over 80% today. (1, 2) Advances have been even more impressive for the most common childhood cancer, acute lymphoblastic leukemia (ALL), for which cure rates have improved from

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<10% in 1960 to over 90% today (3). Yet cancer remains the leading cause of death by disease in children in the developed countries, and the toxicity associated with contemporary therapy adversely affects quality of life during and after treatment (4). Thus, it is imperative that we harness the power of today's science and technology to develop more effective and less toxic treatments for children with cancer.

There has been much written about the potential of "precision medicine" in oncology, using data from whole genome, whole exome, whole transcriptome and/or whole methylome interrogation to select the optimal treatment for individual patients, based on both germline variants and the nature of somatic mutations and not merely the histology and staging of a patient's tumor (5–7). Indeed, it was on this basis that the US NCI launched the MATCH (Molecular Analysis for Therapy Choice) clinical trial, within which adults whose tumors were found to have mutations in either *PIK3CA* or *FGFR* or over-expression of *HER2* (excluding breast and gastric cancers) were treated with agents targeting these mutated genes/pathways (i.e., taselisib, AZD4547 or ado-trastuzumab emtansine, respectively). However, the initial results were disappointing with only partial responses in just 10% of patients given the FGFR inhibitor or the HER2 inhibitor and no objective response with the PIK3CA inhibitor (8). The disappointment was offset somewhat by the fact that many of these patients had not responded well to extensive chemotherapy prior to being enrolled on the MATCH trial. Likewise, the initial enthusiasm for using tumor mutation burden (TMB) determined by whole-exome sequencing as a biomarker for identifying non-small cell lung cancer (NSCLC) patients more likely to respond to PD-1 inhibitors (e.g., pembrolizumab) has been dampened by disappointing results in follow-up prospective clinical trials and by the inability to assess TMB in a high percentage (~30–40%) of patients with NSCLC (9). These findings are a clear signal that we are in the early days of "precision oncology", and this is especially true in pediatric oncology where the number of eligible patients is small and only a few studies have been completed.

Recent attempts to improve precision medicine strategies have included the use of drug combinations based on tumor DNA sequencing (I-PREDICT), sequencing of circulating tumor cells (TARGET) and sequencing tumor DNA coupled with RNA sequencing of adjacent normal tissue (WINTHER) (11). While there were some encouraging responses observed in previously treated patients, only a small minority of patients had objective responses (4–11%). These findings are consistent with the SHIVA trial that found no difference in progression-free survival in previously treated patients with metastatic cancers, after treatment with molecularly targeted therapies compared to physician's choice of treatment (10).

Nonetheless, the number of MATCH-style trials for childhood cancers is growing, including PROFYLE in Canada, ESMART across Europe, and NCI Pediatric MATCH in the US. The US pediatric version of MATCH currently includes ten targeted therapeutics, inhibiting *ALK, BRAF, EZH2, MEK, TRK, PARP, ERK, PI3K/mTOR, CDK4/6*, or *FGFR* signaling pathways (12). In addition to scientific discoveries fueling these potentially exciting trials, legislative initiatives such as RACE for Children Act and the STAR Act are boosting efforts and interest in testing novel agents in pediatric populations, although these studies are not without challenges. There is also great interest in using genomics to guide the "repurposing"

of FDA approved medications as a less expensive and more expedient strategy for expanding treatment for many diseases, including childhood cancers (13).

Glass Half Full

Enthusiasm for targeted therapies for childhood cancers is bolstered by promising results in *BCR-ABL1* ALL, for which the addition of an ABL tyrosine kinase inhibitor to conventional combination chemotherapy markedly improved cure rates from ~30% in historical controls to ~ 60% (14). This treatment advance was subsequently extended beyond the 2–4% of childhood ALL cases with the *BCR-ABL1* fusion, when it was discovered that an additional ~10–15% of pediatric ALL cases have *BCR-ABL1-like ALL* with a gene expression pattern resembling leukemia with the *BCR-ABL1* fusion (15, 16). The underlying genetic mechanisms of *BCR-ABL1*-like ALL have now been largely elucidated; about 50% of these cases have *CRLF2* rearrangements with or without *JAK2* mutations and among the remaining cases, 15–20% have ABL1-class fusions, which exhibited *in vitro* sensitivity to ABL tyrosine kinase inhibitors (17). Another 10 to 15% have *JAK2* or *EPOR* rearrangements or other *JAK-STAT* mutations and exhibited *in vitro* sensitivity to JAK inhibitors (17). Ongoing clinical trials are assessing whether the addition of these agents to conventional chemotherapy will translate into improved cure rates for *BCR-ABL1*-like ALL with targetable lesions, as was observed for *BCR-ABL1* ALL. These discoveries nicely exemplify how genomic studies can identify new subtypes of ALL and establish the scientific basis for selectively incorporating new “targeted” agents into the treatment of patients whose cancer harbors specific somatic mutations.

Similarly, genomic studies have identified multiple subtypes of medulloblastoma (MB), a common type of malignant brain tumor in children (18). The WHO has incorporated consensus criteria to define four major subtypes of MB based on genomic characterization: WNT abnormalities, sonic hedgehog (SHH) abnormalities, and two other distinct groups (Group 3 with high *MYC* amplification and Group 4 that harbors a variety of genetic abnormalities), and treatment today is guided by integration of molecular genetics, histomorphology, and imaging to risk-stratify patients. Clinical trials are currently testing whether escalation of therapy (irradiation, chemotherapy) in high-risk patients or de-escalation of therapy for lower-risk patients can improve treatment outcomes. There are also ongoing studies in patients with SHH-MB to assess the efficacy of targeted SHH inhibitors (that can compromise skeletal development) in skeletally mature patients. Also, inherited germline polymorphisms in *GST-M1/T1* have been associated with increased neuropsychological morbidity after craniospinal irradiation in children with MB (19). In a different type of brain tumor, glioblastoma, somatic hyper-methylation of the O^6-methylguanine-DNA methyltransferase (*MGMT)* gene promoter has been associated with a better response to alkylating agents, including temozolomide, in both children and adults (20–23).

These are still early days of using genomics to tailor the nature and intensity of treatment for pediatric ALL and brain tumors, and ongoing studies are assessing novel cellular therapies, including CAR T-cell therapy targeting either CD19 in B-lineage ALL or HER2 in a subset of MB expressing this epitope.

Likewise, genomic studies are providing new insights and potential novel therapeutic strategies for several pediatric solid tumors. For example, *MYCN, TRK* and *ALK* have pathologic and prognostic relevance in pediatric neuroblastoma, and there are early-stage clinical trials to assess the potential of ALK inhibitors (e.g., crizotinib) for treating ALK-mutated neuroblastomas, with newer generation ALK inhibitors (lorlatinib) showing greater promise in model systems. There have been similar advances with other pediatric solid tumors, including Ewing sarcoma and osteosarcoma, where genomic studies are pointing to new therapeutic targets, some of which are being assessed in early stage clinical trials (24). There have also been promising results using tropomyosin receptor kinase (TRK)-inhibitors (e.g., larotrectinib) in treating a diverse spectrum of pediatric solid tumors with chromosomal rearrangements creating *TRK*-fusions (25).

It remains to be seen whether treatment advances will emerge from ongoing clinical trials that are deploying various genomic methods to identify additional therapeutic targets in pediatric solid tumors (e.g., INFORM) (26). Early results in some pediatric cancers with a dismal prognosis (e.g., diffuse intrinsic pontine glioma) indicate that this approach can reveal previously unrecognized targets for which medications are currently available (27).

And of course there are very well-established examples of using inherited germline variants to guide the selection of appropriate dosages of chemotherapy (e.g., *TPMT* and *NUDT15* to guide thiopurine dosing), or in guiding the use of ancillary medications in pediatric cancer patients, including C*YP2C19* for voriconazole dosing and *CYP2D6* for codeine analgesia. (5) There have also been important advances in building active clinical decision support into the electronic health record, to alert clinicians to the importance of pharmacogenomics for high-risk medications, using evidence-based criteria developed by the Clinical Pharmacogenetics Implementation Consortium (CPIC) (5). It is also not uncommon for inherited functional variants to be present in genes encoding the targets of anticancer agents (28).

Somatic genetic and epigenetic analyses are also providing new insights into the genomic mechanisms of cancer cell resistance to conventional and targeted anticancer agents and revealing potential strategies to mitigate resistance (29–31).

Indeed, the glass is approaching half-full at this stage, with genomics providing deeper insights into disease pathogenesis, and offering improved methods for discovering new targets, assigning prognosis, guiding the intensity of treatment and/or selecting more-targeted chemotherapy for some diseases.

Glass half empty

The above recent progress notwithstanding, the reality is that “precision oncology” is in its infancy for both adult and pediatric cancers. Although genomics provides important diagnostic and therapeutic insights to improve treatment outcome for some malignancies, there is currently a paucity of rigorous evidence of this success for most pediatric cancers. There is promise, but scant evidence.

Therefore, in the coming decade precision oncology must continue to move forward within the context of prospective clinical trials. Yet even within clinical trials, there is often reluctance to define *a priori* the precise genetic abnormalities that will be used to guide treatment decisions, including the selection of medications. Some argue this is understandable, because the body of evidence on which somatic mutations justify changes in treatment is not yet clearly defined. And while there are often "hot spots" for mutations that activate or inactivate critical cancer genes, new driver or cooperative mutations are constantly being discovered as more patient tumors are sequenced and it is extremely challenging to characterize their functional consequences in real-time to determine their impact on drug response. Unfortunately, this often leads to clinical trials with vaguely defined criteria, which risks heterogeneity in treatment decisions depending on who is interpreting the data for any given patient. Furthermore, there are often mutations in multiple genes within the same tumor (Figure 1), making it unclear which mutations should drive treatment decisions and the sequence in which multiple targeted agents should be given has not been rigorously defined. Furthermore, it does not help that most CLIA-compliant genome sequencing services merely report out all mutations in a defined set of "cancer genes" (e.g., COMIC genes), leaving it to the treating clinicians to determine the therapy to be prescribed. This approach is comparable to what is done for tests like blood glucose; almost never do the clinical diagnostic laboratories recommend treatment, they just report out the result and let the treating physician decide what to do. In the case of hyperglycemia, the path toward a precise diagnosis is relatively straightforward, and there is typically little urgency in initiating optimal treatment. But this is not the case when using multiple cancer genome mutations to select optimal cancer therapy for an individual patient. One could argue that CLIA-compliance with genome sequencing is no more important than rigorous evidence-based interpretation of genome sequences, yet the latter is left to flounder outside the CLIA structure, often without strict quality controls. A carefully-designed process for establishing clinical guidelines for using somatic genome variants to direct cancer therapy (similar to CPIC for germline pharmacogenomics) is needed to ensure rational deployment of precision medicine in oncology. Evidence-based artificial intelligence coupled with electronic clinical decision support may hold the answers in the coming decade.

Pediatric precision oncology is also being slowed by the lack of interest within the pharmaceutical industry to develop novel agents that target genes commonly mutated in childhood cancers. The reasons are sadly understandable, as these companies prioritize making a profit, and the number of cases of any childhood cancers pales in comparison to the number of cases of lung cancer, breast cancer or most other adult malignancies. Plus, children are smaller, and thus require fewer milligrams of therapy, all of which makes the financial incentives *de minimis* in the for-profit world. This is nicely exemplified by the development of ALK inhibitors (e.g., crizotinib). ALK mutations (structural variants) were originally discovered in 1994 in a pediatric lymphoma, hence anaplastic lymphoma kinase (32). But pharma had no interest in developing an ALK inhibitor until *ALK* was found to also be activated via a chromosomal translocation in non-small cell lung cancer, 13 years later (2007). There are now five different ALK inhibitors approved by the FDA, with others under development, although none has yet been approved for childhood cancers. It is unclear whether the coming decade will yield incentives or regulatory requirements for

pharmaceutical companies to develop targeted agents for childhood cancers, but little has happened in the decade since the Institute of Medicine report on the failure of pharma to develop new medications for childhood cancers (33). It is hard to be optimistic that this will soon change.

Prospectus

Indeed, in many ways the glass now seems only half full, but the glass is constantly growing due to advances in science and technology that are rapidly expanding our universe of knowledge and challenging our ability to translate this into more effective and less toxic therapy for childhood cancers. Clinical pharmacology is poised to play a critical role in both the discovery and development of new targeted anticancer agents and their translation into better treatment. Over the coming decade, clinical and basic pharmacologists should rise to this challenge (and opportunity) to expand the depth of our science and the bandwidth of our translational capacity, if we are to optimize the use of “precision medicine” to advance the treatment of childhood cancers.

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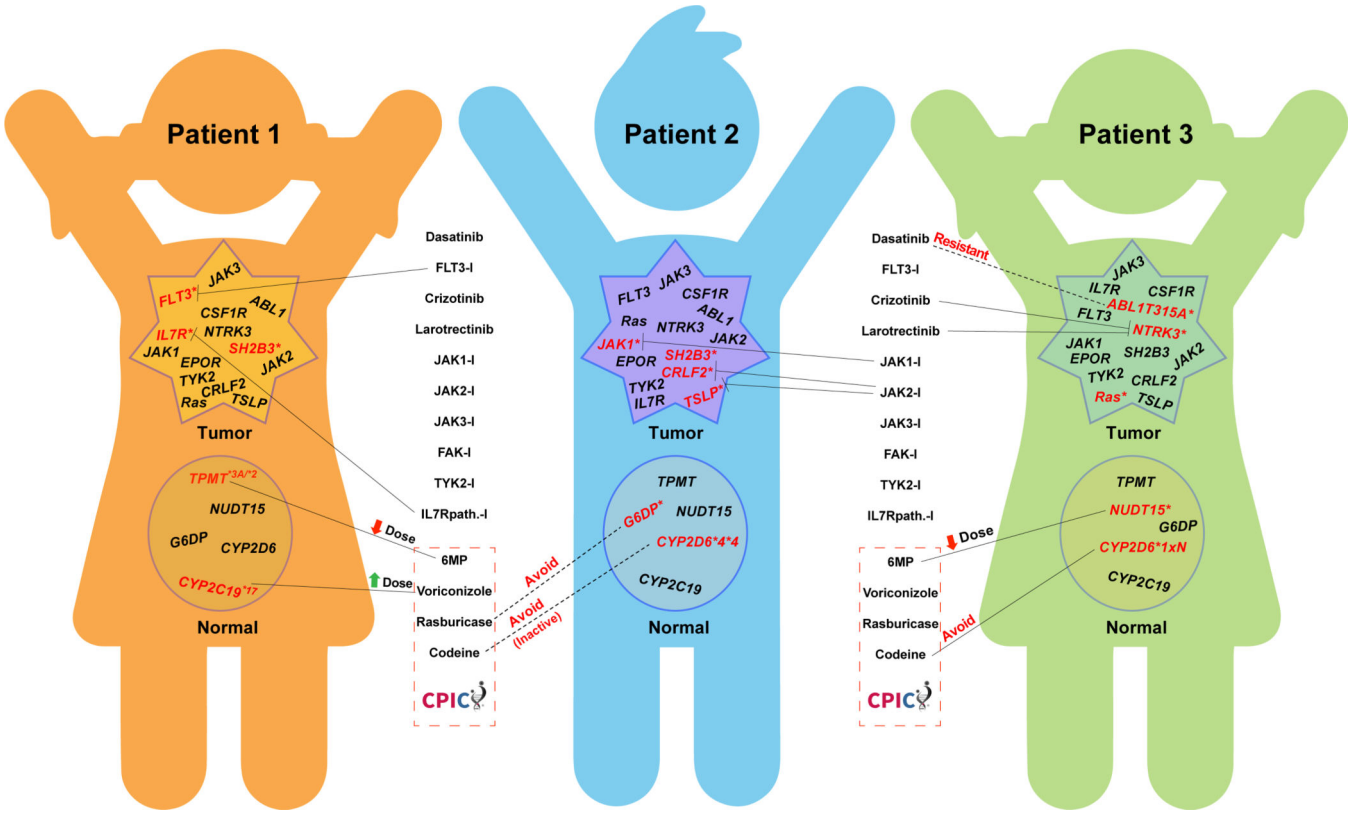

Figure 1. Complexity in selecting optimal medications based on combinations of germline and somatic genome variation in cancer.

Somatic (tumor) and germline (normal) genome variation is reflected for three hypothetical patients with *BCR-ABL1*-like acute lymphoblastic leukemia (ALL), based on actual genome variants documented from sequencing patients with this disease (17). For each hypothetical patient, genes indicated have already been shown to have functional alterations in ALL (mutations or structural alterations in leukemia cells, inherited variants altering function in germline DNA), and those with mutations in each patient are indicated in red font with an asterisk. Somatic variants are often activating, whereas germline genes are typically loss-of-function (*TPMT, NUDT15, CYP2D6*) or more rarely gain-of-function (*CYP2C19* and *CYP2D6* duplication alleles). Potential selection of medications targeting somatic mutations is based on *in vitro* or *in vivo* activity of each medication against target proteins. Multiple variants often occur in the same leukemia cell, as documented in prior sequencing studies (17), and often only a subset are treated, as depicted for each patient. All inherited germline variants are essentially always present in the tumor (not depicted). Selection of optimal therapy using inherited germline variants follows evidence-based CPIC guidelines (for medications below the dotted red line). A substantial number of additional somatic and inherited genome variants are known to exist in this disease, adding further complexity to evidenced-based selection of optimal treatment.