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Precision Medicine in Pediatric Oncology- Is it the Way Forward?

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ABSTRACT

Precision medicine is currently an emerging approach for the treatment of childhood cancer. The use of improved molecular diagnostic techniques has facilitated the identification of actionable molecular targets and hence additional therapeutic opportunities. Next generation sequencing (NGS) has revolutionized our understanding of pediatric cancer and fueled the personalized approach to cancer treatment. Treatment of patients with pediatric cancer is not synonymous with treatment in a mini adult. Pediatric cancers have different genetic constitution and fewer molecular targets as compared to adult tumors. This overview discusses the diagnostic and therapeutic advancements along with some of the important clinical implications and the future prospects of precision medicine in pediatric oncology

KEY WORDS: Precision Medicine, Targeted Therapy, Individualized Medicine, Pediatric Cancer

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INTRODUCTION

The management of patients with pediatric tumors can be sometimes challenging. With improved outcomes and increased overall survival (OS) the main challenge lies in limiting the long term side effects therapy. Recent progress made in molecular diagnostic approaches has led to the concept of "personalized" approach in cancer treatment. The use of this novel approach based on molecularly actionable targets has revolutionized cancer treatment in children. Knowing the fact that cancer is a genomic disease has been the foundation of molecularly targeted therapy (MTT) and precision medicine in oncology [1,2].

Although the initial experiments in precision treatment were mostly in adult patients, currently it is rapidly gaining practical momentum in childhood cancer treatment [3].The scope of application of precision medicine has now included many difficult to treat refractory cancers, relapsed disease and some rare unusual cancers with non- characteristic morphology. However, there are still many caveats in selecting optimal targets, designing effective drugs, identifying appropriate combination therapies and overcoming resistance to therapy and hence is the need of further well designed clinical research

DISCUSSION

The current concepts in treatment of children with cancer is focused on improving outcomes in those with aggressive disease and limiting the serious short and long term side effects of multimodality treatment. Impressive progress in cancer research has elucidated the pathogenetic mechanisms driving the malignant phenotype. Activation of proto-oncogenes, repression of tumor suppression genes, genetic mutations in somatic cells, deregulation of signaling pathways can lead to abnormal cell proliferation, increased cellular survival under stress and avoidance of apoptosis, thereof leading to malignant phenotypes. These hallmarks are unique to cancer cells and can be used as potential therapeutic targets, thus minimizing the side effects arising due to destruction of normal cells.

Diagnostic advancements in identification of actionable targets:

Pediatric cancers harbor less mutational burden in comparison to adults. Also, the molecular alterations seen in childhood cancer patients are distinctive from adults. Many molecular or genetic assays that are currently available like gene testing, fluorescent in situ hybridization (FISH), real-time polymerase chain reaction (RT-PCR), single nucleotide polymorphism (SNP) based microarrays are more robust than conventional cytogenetic methods. However, it's the genetic

sequencing that has really set the stage for precision clinical trials in oncology.

Next generation sequencing (NGS) is a rapid, large scale DNA sequencing technology that allows for screening the whole genome, the exons within all known genes called whole exome or only the exons of selected genes called clinical exome or target panel. The principle of NGS is similar to Sanger sequencing, however it allows for 'massively parallel sequencing' of the entire genome of interest in a single run. It can identify small insertions/deletions (which are beyond the scope of detection by conventional methods), point mutations and SNP. Alongwith computational tools to analyze data it can also identify copy number variations (CNV), single nucleotide variants (SNV), gene fusion and other targetable mutations [4]. NGS is currently being employed as one of the crucial steps for identification of genomic profile characterizing the cancer. Incorporating sequencing can enhance the specificity in diagnosis especially for tumors with indistinct histology and also allow the oncologist to tailor therapy based on molecular targets. Though genetic sequencing studies have added a new dimension to pediatric cancer treatment, only few of these approaches are being done by commercial laboratories to guide clinical practice [5]. The clinical utility of these tests is further limited by the longer turn-around time (TAT) and humongous costs; especially in resource constraint setting of low and middle income countries (LMIC). Thus, the best practices of when and how to use NGS in routine clinical practice are still being elucidated. Although many genetic variants have known clinical implications, but the prognostic significance of many recurring genomic lesions is still not known.

Current clinical applications of precision medicine in pediatric oncology:

Though molecular profiling is being advocated for all pediatric cancers, it is imperative to identify patient groups that will immensely benefit with the use of MTT. The most promising clinical applications of tumor sequencing is being highlighted for tumor relapse/metastasis, undifferentiated cancers, cancer predisposition syndromes and malignancies requiring integrated morphological and molecular diagnosis, like leukemias and brain tumors [6].

In the recent times cancer therapy is mostly risk adapted and response based. This has been made possible with the use of variety of genetic or molecular assays in diagnosis, risk assessment and measurement of disease response. Most contemporary pediatric leukemia protocols stratify patients in different risk groups depending on in vivo response to steroid therapy and post induction minimal residual disease (MRD). Advancement in cytogenetic analysis and increasing use of NGS has determined certain risk groups in leukemia, characterized for instance by specific chromosomal translocations, that are more refractory to chemotherapy alone and require more intensive therapies like allogeneic stem cell transplant (SCT) as a part of consolidation.

Conventional risk stratification approaches that were being used for pediatric solid tumor treatment included extent of tumor, site, size, spread and histologic subtype. Cytogenetic method like conventional karyotyping was used for molecular characterization of cancer cells, highlighting the numerical and structural chromosomal anomalies in cancer cells.

Genomic profiling has become pertinent in the evaluation of brain tumors and has also been included in the current World Health Organization (W.H.O) classification of Central Nervous System (C.N.S) tumors [7].

Detection of circulating tumor DNA ("liquid biopsies") is an upcoming non-invasive diagnostic and disease monitoring tool for solid tumor. This concept is now being evaluated for Neuroblastoma and Ewing sarcoma [8,9]

Therapeutic applications of precision medicine in pediatric hemato-lymphoid malignancy:

Most of the targeted therapies, with some notable exceptions, in the pediatric age group are still under clinical trials. Thus, the data on clinical efficacy and toxicity profile is sparse.

Tyrosine kinase inhibitors (TKI):

Aberrant activation of tyrosine kinases leads to malignant transformation. This deregulated activation can be due to activating mutations or inactivating mutations of the suppressor genes. The reciprocal translocation between chromosome 9 and 22 forms the Philadelphia (Ph) chromosome [t 9;22] which is the hallmark of Chronic Myeloid Leukemia (CML) and Ph ALL. This BCR-ABL gene fusion causes constitutive activation of tyrosine kinases. The TKI discovery is exemplary in the field of precision medicine. In 2001, Imatinib (GLEEVAC) received United States Food and Drug Administration (US FDA) approval for treatment of CML patients in chronic (CP), accelerated (AP) or blast crises (BC) phase [10]. In 2011, it was approved for use in pediatric Ph ALL alongwith cytotoxic chemotherapy [10]. In November 2017, Dasatinib (SPRYCEL) was FDA approved for use in children with CP CML. The second generation TKI, Nilotinib, which exhibits extended kinase selectivity, received FDA approval in March 2018 as a first line therapy for the treatment of newly diagnosed children with CML CP and as a second line therapy for patients resistant or intolerant to previous TKI [11]. Patients age 1 year and above are eligible to receive this drug. There are various short and long term side effects, which should be monitored during TKI therapy. Endocrine problems and growth issues should be particularly monitored in pediatric patients.

Differentiation agents: The introduction of differentiation therapy as a standard of care in treatment of Acute Promyelocytic Leukemia (APL), has led to the evolution of

APL from a rapidly fatal disease to one of the most curable forms of Acute Myeloid leukemia (AML). APL is characterized by balanced translocation t (15; 17) (q24.1;q21.2) resulting in fusion of ProMyelocytic Leukemia gene (*PML*) and Retinoic Acid Receptor Alpha gene (*RARA*) to generate the PML-RARA oncoprotein. This protein is the driver of APL causing differentiation arrest at the promyelocytic stage. Unlike the conventional cytotoxic chemotherapy All trans retinoic acid (ATRA) in combination with Arsenic Trioxide (ATO) causes differentiation of APL cells into more mature cells which undergo spontaneous apoptosis. APL represents a prototypical example of a disease in which identification of the actionable molecular target has led to revolutionary improvement in diagnosis, treatment, event free survival (EFS) and overall survival (OS). Beyond APL, differentiation therapy is being investigated in other pediatric cancers, including use as maintenance therapy for high risk Neuroblastoma.

Proteasome inhibitors: The 26 S proteasome is involved in the regulation of cell cycle and apoptosis. The inhibition of proteasome by specific agents serves as a novel target for antitumor therapy. Bortezomib is a reversible inhibitor of proteasome which is being currently used as a part of combination chemotherapy for adults. Currently there is no pediatric indication. However, it is being analyzed in many exploratory clinical trials with promising results. Currently it is being evaluated in combination with conventional chemotherapy for relapsed B-ALL (Phase III), newly diagnosed T-ALL (Phase III), mixed lineage leukemia (MLL) rearranged infant ALL (Phase II), relapsed T-ALL and relapsed MLL rearranged infant ALL (Phase II). The addition of bortezomib does not appear to significantly increase toxicity with any of the chemotherapy backbones evaluated so far.

Janus kinase/signal transducers and activators of transcription (JAK/STAT):

Constitutive activation of the JAK/STAT pathway is linked to advanced tumor growth and metastasis through various mechanisms like enhanced angiogenesis, modulation of tumor stroma, immunomodulation and autonomous tumor growth [12].The inhibition of this signaling was proposed to suppress the pro-inflammatory tumor-microenvironment, thereby preventing tumor progression [13]. Janus Kinases (JAKs 1, 2, 3) are frequently mutated in myeloproliferative neoplasms (MPN), high risk ALL (Ph like ALL and infant ALL) and few subsets of AML [14,15]. Cytokine receptor – like factor 2 rearrangement (CRLF2-R) with concomitant JAK 2 point mutations occurs in 50% of Ph like ALL cases and causes constitutive activation of kinase signaling. Ruxolitinib, which is potent inhibitor of JAK 1, 2 has demonstrated clinical safety and tolerability alongwith post induction chemotherapy in children and adolescents with newly diagnosed high risk (HR) Ph like ALL harboring CRLF2-R/JAK pathway mutation, treated on the non-randomized, 2-part phase 2 study INCB18424-269 (AALL1521; NCT02723994) [16]. Phase I/II trial of Ruxolitinib in adolescents with relapsed/ refractory AML and ALL (NCT 01251965), concluded that it was reasonably tolerated in this group of heavily pre treated patients, with infections as the most important non-hematologic toxicity reported [17]. Pre-clinical studies have provided evidence on the clinical activity of JAK inhibitors in pediatric acute megakaryoblstic leukemia (AMKL) [18].

FMS like tyrosine kinase (FLT3) inhibitors:

FLT3 receptor encodes a class III receptor tyrosine kinase which modulates the survival, proliferation and differentiation of hematopoietic cells. Activating mutations of the *FLT3* gene occur because of either an internal tandem duplication of the juxta-membrane domain (FLT3/ITD) or point mutation of the activation loop domain (FLT3/ALM). FLT3 mutation is seen in approximately 15 % patients with pediatric AML, particularly those with normal cytogenetics. The presence of FLT3-ITD with high allelic ratio (mutant: wild type allele ratio more than 0.4) confers poor prognosis in pediatric AML [19]. Also, FLT3 activation mutation is seen in about 18 % of mixed lineage leukemia rearranged (MLL r)/KMT2A r high risk ALL. KMT2A rearrangement occurs in 80% of infants and 5% children with ALL. This subset of patients are usually refractory to conventional chemotherapy and hence portend a poor prognosis. So far, FLT3 inhibitors have shown limited clinical effectiveness as monotherapy both in AML and ALL. Lestaurtinib, an orally available FLT3 inhibitor, in combination with conventional chemotherapy is being evaluated in a multicentre Phase III study for newly diagnosed KMT2A r ALL (NCT00557193). The safety profile, efficacy and biologically effective dose of this drug is also being evaluated in Phase I/II trial in relapsed/refractory FLT3 mutant AML(NCT00469859). Midostaurin and Quizartinib are other agents that are being evaluated in studies as a single agent for post consolidation therapy in FLT3 mutated AML patients (NCT03591510) and in relapsed refractory AML in combination with reinduction chemotherapy followed by single agent maintainence therapy (NCT03793478).

ALK (Anaplastic lymphoma kinase)inhibitors: The ALK-NPM (Nucleophosmin) fusion transcript is involved in the pathogenesis of a subset of anaplastic large-cell lymphoma (ALCL) [20]. *ALK* rearrangement, mutation, or amplifican is elucidated in a variety of tumors, including neuroblastoma, inflammatory myofibroblastic tumor (IMT), and non-small-cell lung cancer (NSCLC)[21]. Crizotinib is a dual inhibitor of ALK and MET. It is the first ALK inhibitor to be tested in phase I–II clinical trials of pediatric patients with ALCL [22]. Crizotinib is well tolerated in pediatric patients and showed excellent antitumor activity in patients with ALCL and IMT [21].

Conclusion: Precision medicine is an arena of highly active research, in pediatric oncology. Majority of the research efforts are being directed to the development of novel targeted agents for the treatment of patients with relapsed or refractory disease. Inhibition of transcriptional programs and epigenetic regulation are potential areas being explored in pediatric cancers especially leukemias. The concept of 'synthetic lethality' is an emerging concept of targeted precision for cancers with poor prognosis. This is based on the hypothesis that cancers with loss-of-function mutations become "treatable" when two discrete and unrelated genes are simultaneously targeted. The ultimate goal of precision medicine is to optimize cure rates and reduce therapy related side effects by selectively targeting cancer cells.

REFERENCE:

I. Kalia M. Personalized oncology: Recent advances and future challenges. *Metabolism*. 2013;62(Suppl. 1):S11–S14. doi: 10.1016/j.metabol.2012.08.016.

II. Garraway L.A, Verweij J, Ballman K.V. Precision oncology: An overview. *J Clin Oncol*. 2013; 31:1803–1805. doi: 10.1200/JCO.2013.49.4799.

III. Mendelsohn J. Personalizing oncology: Perspectives and prospects. *J Clin Oncol*. 2013; 31:1904– 1911. doi: 10.1200/JCO.2012.45.3605.

IV. Blumenthal G.M., Mansfield E , Pazdur R. Next-generation sequencing in oncology in the era of precision medicine. *JAMA Oncol*. 2016;2:13–14. doi: 10.1001/jamaoncol.2015.4503.

V. Joseph L, Cankovic M, Caughron S et al. The spectrum of clinical utilities in molecular pathology testing procedures for inherited conditions and cancer: a report of the Association for Molecular Pathology. *J Mol Diagn*. 2016;18:605–619.

VI. Ahmed A.A, Vundamati S.D, Farooqi S.M et al. Precision Medicine in Pediatric Cancer: Current Applications and Future Prospects. *High Throughput*. 2018 Dec; 7(4): 39.

VII. Louis DN, Perry A, Reifenberger G, et al. The 2016 World Health Organization classification of tumors of the central nervous system: a summary. *Acta Neuropathol*. 2016;131(6):803-820.

VIII. Lodrini M, Sprussel A, Astrahantseff K, et al. Using droplet digital PCR to analyze MYCN and ALK copy number in plasma from patients with neuroblastoma. *Oncotarget*. 2017;8:85234–85251

IX. Krumbholz M, Hellberg J, Steif B, et al. Genomic EWSR1 fusion sequence as highly sensitive and dynamic plasma tumor marker in Ewing sarcoma. *Clin Cancer Res*. 2016; 22:4356–4365

X. FDA Approval for Gleevec for Children with Ph+ ALL, Oncology Times: February 25th, 2013 - Volume 35 - Issue 4 - p 12. doi: 10.1097/01.COT.0000427834.60711.5c

XI. Novartis drug Tasigna® approved by FDA to treat children with rare form of leukemia [news release]. Basel, Switzerland: Novartis; March 22, 2018. https://www.novartis.com/news/media-releases/novartis-drug-tasignar-approved-fda-treat-children-rare-form-leukemia

XII. Jarnicki A, Putoczki T, Ernst M. Stat3: linking inflammation to epithelial cancer – more than a "gut" feeling? *Cell Div*. 2010;5:14. doi: 10.1186/1747-1028-5-14. 1747-1028-5-14

XIII. Groner B, Von Manstein V. Jak Stat signaling and cancer: opportunities, benefits and side effects of targeted inhibition. *Mol Cell Endocrinol*. (2017) 451:1–14. doi:10.1016/j.mce.2017.05.033

XIV. Kiladjian JJ. The spectrum of JAK2-positive myeloproliferative neoplasms. *Hematol Am Soc Hematol Educ Program*. 2012:561–566. doi: 10.1182/asheducation-2012.1.561

XV. Roberts KG, Li Y, Payne-Turner D, et al. Targetable kinase-activating lesions in Ph-like acute lymphoblastic leukemia. *N Engl J Med*. 2014;371:1005–15. doi: 10.1056/NEJMoa1403088

XVI. Tasian K.S, Assad A, Hunter S.D, et al. A Phase 2 Study of Ruxolitinib with Chemotherapy in Children with Philadelphia Chromosome-like Acute Lymphoblastic Leukemia (INCB18424-269/AALL1521): Dose-Finding Results from the Part 1 Safety Phase. *Blood*. 2018; 132 (Supplement 1): 555

XVII. Pemmaraju N, Kantarjian H, Kadia T, et al. A phase I/II study of the Janus kinase (JAK)1 and 2 inhibitor ruxolitinib in patients with relapsed or refractory acute myeloid leukemia. *Clin Lymphoma Myeloma Leuk*. 2015;15:171–176. doi: 10.1016/j.clml.2014.08.003

XVIII. Drenberg CD, Shelat A, Dang J, et al. A high-throughput screen indicates gemcitabine and JAK inhibitors may be useful for treating pediatric AML. *Nat Commun*.2019;10:2189. doi: 10.1038/s41467-019-09917-0

XIX. Meshinchi S, Alonzo TA, Stirewalt DL, et al. Clinical implications of FLT3 mutations in pediatric AML. *Blood*. 2006 Dec 1;108(12):3654-3661. doi: 10.1182/blood-2006-03-009233.

XX. Morris SW, Kirstein MN, Valentine MB et al. Fusion of a kinase gene, ALK, to a nucleolar protein gene, NPM, in non-Hodgkin's lymphoma. *Science*. 1994; 263: 1281–1284.

XXI. Mossé YP, Laudenslager M, Longo L et al. Identification of ALK as a major familial neuroblastoma predisposition gene. *Nature*. 2008; 455: 930–935.

XXII. Mossé YP, Lim MS, Voss SD et al. Safety and activity of crizotinib for paediatric patients with refractory solid tumours or anaplastic large-cell lymphoma: a Children's Oncology Group phase 1 consortium study. *Lancet Oncol*. 2013; 14: 472–480.