Commentary

Top advances of the year: Pediatric oncology

Alberto S. Pappo, MD ; Seth E. Karol, MD ; and Kelsey C. Bertrand, MBBS

Accelerated discovery and collaborative research continue to highlight the remarkable progress that has been made in the diagnosis and treatment of pediatric cancers. This manuscript highlights important discoveries on how precision oncology is being incorporated into the diagnosis and treatment of childhood cancer at the national level to identify promising new therapies using a tumor-agnostic approach. In addition, we have highlighted three articles that incorporate genomics and cell-free DNA to better classify, monitor and incorporate risk-based therapies for children with medulloblastoma. Finally, we highlighted the important role of monclonal antiobody therapy in the treatment of recurrent B-cell leukemia and newly diagnosed high-risk neuroblastoma. ***Cancer* 2022;0:1-4**. *© 2022 American Cancer Society.*

PRECISION ONCOLOGY FOR ALL PEDIATRIC PATIENTS

Recurrent disease remains a major cause of mortality among children with cancer. Genomic and transcriptomic analyses have revealed that approximately 45% of driver genes in pediatric tumors are also seen in adult cancers, and ≤50% of pediatric cancers have a potentially druggable event. However, access to next-generation sequencing platforms and molecularly targeted therapies limits the ability to treat children with recurrent cancer via precision medicine approaches.

The Children's Oncology Group (COG) Pediatric Molecular Analysis for Therapy Choice (MATCH) trial[1] was developed as a national framework to investigate molecularly targeted therapies in patients aged 1–21 years with refractory solid tumors, non-Hodgkin lymphoma, or histiocytic disorders. After initial tumor recurrence, tumor tissue was subjected to sequencing via a 159–cancer gene panel and limited immunohistochemical assays to identify potential targets that could be amenable to pharmacologic intervention. Tumor screening was completed in 1000 samples (94.7%): 31.5% had an actionable alteration, and 28.4% and 13.1% of the patients were assigned and enrolled, respectively, in one of 13 treatment arms. More than 70% of those patients had extracranial solid tumors. Alterations in the MAPK pathway were the most common actionable alterations (11.2%); other actionable alterations included *BRAF* fusions/mutations (4.2%), *SMARCB1* loss/mutations (3.9%), *CDK4* amplification (3.1%), *FGFR* mutations/fusions (2.9%), and *NF1* mutations (2.4%). Nonactionable gene alterations were seen in 347 tumors, the most common being *TP53* mutations (11.8%), *MYCN* amplification (2.7%), *CTNNB* mutations (2.1%), and *MYC* amplification (1.8%).

The MATCH trial demonstrated the feasibility of nationwide screening and centralized testing for recurrent pediatric cancers by using a limited tumor-agnostic approach. This work has paved the way for future studies of combination therapies and more comprehensive tumor-testing strategies[2] such as the Molecular Characterization Initiative of the National Cancer Institute, which will provide, free of charge, an integrated genomic analysis (methylation and RNA fusion analysis and whole exome sequencing) of pediatric patients with brain tumors, sarcomas, and rare cancers with a faster turnaround time; this will greatly enhance the diagnostic accuracy and our ability to identify genetic aberrations that may be amenable to therapeutic interventions.

SOLID TUMORS

Incorporating immunotherapy into the frontline treatment of high-risk neuroblastoma

Adding a chimeric anti-GD2 antibody (dinutuximab) during maintenance therapy for high-risk neuroblastoma improves 5-year outcomes[3]; however, nearly half of these patients are refractory to therapy or experience relapse and die of their disease.[4] Investigators at St. Jude Children's Research Hospital conducted a prospective, single-institution, phase 2 trial combining a novel humanized anti-GD2 monoclonal antibody (hu14.18 K322A) with chemotherapy during induction in 64 patients with newly diagnosed high-risk neuroblastoma.[5] Patients received six cycles of induction chemotherapy with topotecan, cyclophosphamide, cisplatin/etoposide, and doxorubicin/cyclophosphamide/vincristine as previously described[4] in combination with hu14.18K322A (four daily doses), granulocyte-macrophage colony-stimulating factor, and low-dose interleukin 2. Tumors were

Corresponding Author: Alberto S. Pappo, MD, Department of Oncology, St. Jude Children's Research Hospital, 262 Danny Thomas Pl, Memphis, TN 38105, USA (alberto.pappo@stjude.org).

Department of Oncology, St. Jude Children's Research Hospital, Memphis, Tennessee, USA

DOI: 10.1002/cncr.34425, **Received:** June 1, 2022; **Revised:** July 4, 2022; **Accepted:** July 18, 2022, **Published online** Month 00, 2022 in Wiley Online Library (wileyonlinelibrary.com)

resected after at least two cycles of therapy, and this was followed by consolidation therapy with a busulfan/melphalan conditioning regimen. Local radiotherapy and postconsolidation therapy with hu14.18K322A, granulocyte-macrophage colony-stimulating factor, interleukin 2, and isotretinoin were administered as previously described.[3] The regimen was well tolerated with a continuous infusion of narcotics. The four major findings of this trial were as follows:

1. Partial responses or better were seen after two cycles of chemoimmunotherapy in 42 of 63 patients (66.7%); this is significantly better than the 39% response rate reported in a COG trial using the same initial chemotherapy regimen without the antibody.[6]
2. No patients experienced progressive disease during induction therapy.
3. An end-of-induction partial response or better was seen in 60 of 62 evaluable patients (96.8%); this compares favorably to the end-of-induction responses in previous COG and European International Society of Pediatric Oncology Neuroblastoma Group trials (75%–80%).[4,7]
4. The 3-year event-free survival (EFS) and overall survival (OS) rates were 73.7% and 86%, respectively, which are higher than those measured in a previous high-risk neuroblastoma trial.[5]

These encouraging results warrant further validation in a larger prospective, randomized trial.

Brain tumors

Pediatric brain tumors are the leading cause of cancer-related death in children despite aggressive management with multimodal therapies.[8] In 2021, major advances were made in understanding the importance of molecular subgroup risk stratification and residual disease monitoring in the clinical care of patients with medulloblastoma.

In a phase 3 randomized clinical trial (ACNS0332),[9] 261 patients with high-risk medulloblastoma (metastases, incomplete surgical resection, or diffuse anaplasia) were randomized to receive weekly vincristine with or without daily carboplatin (35 mg/m^2) during radiation therapy (36-Gy craniospinal radiation therapy) followed by maintenance therapy with six cycles of cisplatin, cyclophosphamide, and vincristine with or without 12 cycles of isotretinoin. The 5-year EFS and OS rates for the whole cohort were 62.9% and 73.4%, respectively. The isotretinoin randomization was discontinued early because of futility. Although the 5-year EFS and OS rates were similar for patients in the carboplatin randomization, an analysis of 231 molecularly stratified patients identified group 3 medulloblastoma (n = 79) as a subgroup that benefited from the addition of carboplatin (5-year EFS, 73.2% vs. 53.7%; 5-year OS, 82.8% vs. 63.7%). Hematological toxicities were greater in the carboplatin arm during induction therapy. This study highlighted the importance of an integrated clinical and molecular approach for optimizing risk stratification in medulloblastoma and the potential therapeutic benefit of carboplatin in molecularly defined group 3 patients.

In another phase 3 clinical trial (SJMB03),[10] 330 patients with newly diagnosed medulloblastoma were stratified into average-risk (69%) and high-risk (31%) groups based on their metastatic status and extent of surgery (gross total/nearly total resection vs. subtotal resection). Among average-risk patients, the 5-year progression-free survival (PFS) rates were 100% for the wingless (WNT) subgroup, 77.5% for the sonic hedgehog (SHH) subgroup, 66.7% for group 3, and 87.3% for group 4. Among high-risk patients, the 5-year PFS rates were 100% for the WNT subgroup, 25% for the SHH subgroup, 40.6% for group 3, and 68.1% for group 4 (p = .0017). The authors were able to identify additional prognostic factors, which included three low-risk groups with excellent outcomes with PFS > 90% (the WNT subgroup, the low-risk SHH subgroup, and low-risk groups 3 and 4) and two very high-risk subgroups with PFS < 60% (the high-risk SHH subgroup and high-risk groups 3 and 4). This highlighted the importance of integrating molecular and clinical factors to improve risk-based therapy strategies for children with medulloblastoma.

Liu and investigators[11] performed low-coverage whole genome sequencing to assess more than 450 cerebrospinal fluid (CSF) samples from a large cohort of pediatric patients with medulloblastoma treated in a prospective trial (SJMB03). Of the 105 CSF samples obtained at diagnosis, 67 (63.8%) were positive for measurable residual disease (MRD): 29 of 34 patients with metastatic disease (85%) were MRD+, as were 38 of 71 patients with nonmetastatic disease (54%). Patients whose disease eventually progressed had significantly higher MRD persistence during therapy than those without progressive disease.

The detection of MRD preceded radiographic and/or cytologic relapse by ≥3 months in 16 of the 32 patients (50%) who had experienced a complete response (per radiographic findings) before disease relapse. All 27 CSF samples from patients with persistent disease (per radiographic and/or cytologic findings) were MRD+. Compared with magnetic resonance imaging and CSF cytology, MRD at the end of therapy better risk-stratified treatments

according to PFS. Regardless of the initial subgroup and risk stratification, MRD detection offers an unprecedented opportunity to identify patients who may need additional therapy to decrease their risk of progression.

This is the first study to systematically demonstrate the importance of serial CSF-derived cell-free DNA profiling in detecting MRD in pediatric patients with brain tumors. It provides a foundation for detecting MRD in pediatric brain tumors to monitor relapse and improve the survival of these patients.[11]

LEUKEMIA

In 2021, major advances in treating children with acute lymphoblastic leukemia (ALL) were attributed to the bispecific antibody construct blinatumomab, which targets CD19 on B-cell precursors and CD3 on T cells. Blinatumomab is active and effective in children and adults with relapsed or refractory ALL. The TOWER (the phase 3 randomized open label study investigating the efficacy of the BITE antibody Blinatumomab versus standard of care chemotherapy in adult subjects with relapsed refractory B-precursor acute lymphoblastic leukemia) trial has shown that this novel drug is superior to chemotherapy in adults with relapsed ALL; patients had higher rates of complete remission, MRD– remissions, and prolonged EFS.[12] In alignment with the adult data, the pediatric data demonstrated excellent response outcomes after blinatumomab treatment, particularly in patients with lower burden disease.[13–16] Before 2021, the efficacy of blinatumomab in the context of multiagent chemotherapy for relapsed or refractory leukemia remained unknown. These data were urgently needed because of differing treatment strategies at diagnosis and relapse for pediatric ALL and adult ALL and widely disparate genetic subgroups in these populations.[17] Addressing these differences, clinical trials in North America and Europe tested blinatumomab, which was given as a consolidative strategy for children with high-risk first-relapse B-cell acute lymphoblastic leukemia (B-ALL). Results from two large trials were reported in 2021, and they demonstrated the benefits of this agent.

Advancing the treatment of high-risk first-relapse B-ALL

The COG AALL1331 (the Children's Oncology Group study of Blinatumomab in first relapse of childhood B-lineage acute lymphoblastic leukemia) trial randomized 216 children and young adults with high-risk first-relapse B-ALL to receive either two cycles of blinatumomab or intensive consolidation blocks modeled after the UKALL R3 trial.[18] Patients receiving blinatumomab experienced a lower rate of high-degree toxicity than those receiving consolidation (2% vs. 27%) and also experienced a lower incidence of documented infections, febrile neutropenia, and mucositis. MRD clearance was also superior in these patients after one to two cycles, and this resulted in a higher proportion of patients proceeding to transplantation (70% vs. 43%) and superior EFS (54.4% vs. 39%) and OS (71.3% vs. 58.4%).

A similar trial was conducted in Europe among patients with high-risk first-relapse B-ALL.[19] Patients who had completed reinduction and two cycles of chemotherapy-based consolidation were randomized to receive either blinatumomab or chemotherapy as a third consolidation course; 54 patients were randomly assigned to each treatment arm. Patients receiving blinatumomab had superior EFS and OS in comparison with those receiving a third cycle of chemotherapy. An MRD– status was achieved in 90% of patients treated with blinatumomab but in only 54% of those who received chemotherapy. Fewer serious adverse events were also experienced by the blinatumomab group (24.1% vs. 43.1%).

Together, these trials have established blinatumomab as the new standard of care for consolidation in children with high-risk first-relapse B-ALL. Ongoing and future studies will explore combinatorial therapy with blinatumomab, its use in patients with lower risk first-relapse B-ALL, and the use of this and other new agents in children with newly diagnosed ALL.

ACKNOWLEDGMENT

This work was supported in part by the American Lebanese Syrian Associated Charities.

FUNDING INFORMATION

American Lebanese Syrian Associated Charities.

CONFLICTS OF INTEREST

The authors made no disclosures.

REFERENCES

1. Parsons DW, Janeway KA, Patton DR, et al. Actionable tumor alterations and treatment protocol enrollment of pediatric and young adult patients with refractory cancers in the National Cancer Institute–Children's Oncology Group Pediatric MATCH trial. *J Clin Oncol*. 2022;40(20):2224-2234.
2. Newman S, Nakitandwe J, Kesserwan CA, et al. Genomes for kids: the scope of pathogenic mutations in pediatric cancer revealed by comprehensive DNA and RNA sequencing. *Cancer Discov*. 2021;11:3008-3027.
3. Yu AL, Gilman AL, Ozkaynak MF, et al. Anti-GD2 antibody with GM-CSF, interleukin-2, and isotretinoin for neuroblastoma. *N Engl J Med*. 2010;363:1324-1334.
4. Park JR, Kreissman SG, London WB, et al. Effect of tandem autologous stem cell transplant vs single transplant on event-free survival in patients with high-risk neuroblastoma: a randomized clinical trial. *JAMA*. 2019;322:746-755.
5. Furman WL, McCarville B, Shulkin BL, et al. Improved outcome in children with newly diagnosed high-risk neuroblastoma treated with

chemoimmunotherapy: updated results of a phase II study using hu14.18K322A. *J Clin Oncol*. 2022;40:335-344.
6. Park JR, Scott JR, Stewart CF, et al. Pilot induction regimen incorporating pharmacokinetically guided topotecan for treatment of newly diagnosed high-risk neuroblastoma: a Children's Oncology Group study. *J Clin Oncol*. 2011;29:4351-4357.
7. Granger MM, Naranjo A, Bagatell R, et al. Myeloablative busulfan/melphalan consolidation following induction chemotherapy for patients with newly diagnosed high-risk neuroblastoma: Children's Oncology Group trial ANBL12P1. *Transplant Cell Ther*. 2021;27:490.e1-490.e8.
8. Hossain MJ, Xiao W, Tayeb M, Khan S. Epidemiology and prognostic factors of pediatric brain tumor survival in the US: evidence from four decades of population data. *Cancer Epidemiol*. 2021;72:101942.
9. Leary SES, Packer RJ, Li Y, et al. Efficacy of carboplatin and isotretinoin in children with high-risk medulloblastoma: a randomized clinical trial from the Children's Oncology Group. *JAMA Oncol*. 2021;7:1313-1321.
10. Gajjar A, Robinson GW, Smith KS, et al. Outcomes by clinical and molecular features in children with medulloblastoma treated with risk-adapted therapy: results of an international phase III trial (SJMB03). *J Clin Oncol*. 2021;39:822-835.
11. Liu APY, Smith KS, Kumar R, et al. Serial assessment of measurable residual disease in medulloblastoma liquid biopsies. *Cancer Cell*. 2021;39:1519-1530.e4.
12. Kantarjian H, Stein A, Gokbuget N, et al. Blinatumomab versus chemotherapy for advanced acute lymphoblastic leukemia. *N Engl J Med*. 2017;376:836-847.
13. Zhao Y, Aldoss I, Qu C, et al. Tumor-intrinsic and -extrinsic determinants of response to blinatumomab in adults with B-ALL. *Blood*. 2021;137:471-484.
14. Keating AK, Gossai N, Phillips CL, et al. Reducing minimal residual disease with blinatumomab prior to HCT for pediatric patients with acute lymphoblastic leukemia. *Blood Adv*. 2019;3:1926-1929.
15. Gokbuget N, Dombret H, Bonifacio M, et al. Blinatumomab for minimal residual disease in adults with B-cell precursor acute lymphoblastic leukemia. *Blood*. 2018;131:1522-1531.
16. von Stackelberg A, Locatelli F, Zugmaier G, et al. Phase I/phase II study of blinatumomab in pediatric patients with relapsed/refractory acute lymphoblastic leukemia. *J Clin Oncol*. 2016;34:4381-4389.
17. Roberts KG, Mullighan CG. Genomics in acute lymphoblastic leukaemia: insights and treatment implications. *Nat Rev Clin Oncol*. 2015;12:344-357.
18. Brown PA, Ji L, Xu X, et al. Effect of postreinduction therapy consolidation with blinatumomab vs chemotherapy on disease-free survival in children, adolescents, and young adults with first relapse of B-cell acute lymphoblastic leukemia: a randomized clinical trial. *JAMA*. 2021;325:833-842.
19. Locatelli F, Zugmaier G, Rizzari C, et al. Effect of blinatumomab vs chemotherapy on event-free survival among children with high-risk first-relapse B-cell acute lymphoblastic leukemia: a randomized clinical trial. *JAMA*. 2021;325:843-854.