

## IN FOCUS

# Mobilizing China and the Global Community to Confront the Treatment Desert for Pediatric Solid Tumors



Shuhang Wang<sup>1</sup>, Yale Jiang<sup>1</sup>, Rongshou Zheng<sup>2</sup>, Yue Yu<sup>1</sup>, Wenqiang Wei<sup>2</sup>, and Ning Li<sup>1</sup>

**Summary:** Pediatric solid tumors are distinct clinical entities that impose heavy socioeconomic burden and while their incidence has increased in recent years, treatment options are often limited, with only 27 drugs approved for pediatric solid tumors in the United States, and fewer still, 13, in China. The scale of the unmet medical need is immense and new efforts are urgently needed to develop efficient therapeutics and improve these children's lives.

More than 400,000 children and adolescents are estimated to be diagnosed with cancer each year worldwide (1). Although survival rates for childhood cancers currently exceed 80% in high income countries, the situation is markedly worse in lower- to middle-income countries with the five-year survival rate of pediatric cancers at less than 30%. Moreover, many pediatric cancers are difficult to treat and even in cases of successful treatment, recurrence remains an enormous physical and psychosocial concern for survivors (2). Despite the gains that have been made to decrease overall mortality, these tumors can have lasting impact on the quality of life, in particular, for patients with bone and nervous system cancers.

Although hematologic malignancies continue to be the most common cancers in children, the incidence of solid tumors has increased in recent years. Despite their prevalence, comparatively less attention is paid to the strategic management in this population. The distinct epidemiologic, genetic, and clinical features of pediatric solid tumors also present unique treatment challenges, including a lack of effective therapeutics and the absence of dosage guidelines in many cases.

## THE INCIDENCE OF PEDIATRIC SOLID TUMORS IS RISING IN CHINA

Since 2000, the growth in the annual incidence of pediatric tumors in China has been estimated at 2.8%. Incidence and

survival data for patients with cancer under 18 years old has been collected by the National Central Cancer Registries, integrating data of 348 registries from 2014 to 2018 (Supplementary Table S1; Supplementary Fig. S1). This effort has characterized all 209 cancer types found to have an incidence under 2.5/100,000, the cutoff for rare tumors defined in China (3). Hematopoietic cancer is the most common category of pediatric cancer, accounting for approximately 43.6% of the cases, followed by cancers of the nervous system (13.3%), endocrine system (8.9%), and digestive system (5.6%; Fig. 1A). As for specific cancer types, precursor B/T lymphoblastic leukemia is currently the most dominant, whereas among solid malignancies, astrocytic tumors of the central nervous are the most common, consistent with published data in other countries (4–6). Compared with the United States, China has a higher incidence of reproductive tumors, bone tumors, and epithelial neoplasm, including thyroid and nasopharyngeal carcinomas. Considering the relatively rarity of many individual types of childhood tumors, understanding the prevalence of specific entities in different regions of the world may help avoid misdiagnosis and benefit timely initial treatment.

Of note, bone tumor patients bear the highest mortality rate, followed by neuroblastoma. The overall 5-year relative survival rate is slightly higher in girls than in boys (60.4% vs. 55.7%), although the composition of cancer subtypes is relatively consistent between sexes. Mortality rates have decreased along with the development of cancer therapeutics, but the differences persist by gender (7). Understanding this sex disparity may also help elucidate the underlying mechanisms and improve outcomes.

## LIMITED TREATMENT MODALITIES ARE AVAILABLE

To characterize the current landscape of treatments of pediatric solid tumors we assessed approvals from the FDA and China's National Medical Products Administration (NMPA) database. The FDA has approved 27 drugs for pediatric solid tumors since the early 1950s (Fig. 1B; Supplementary Table S2), ranging from early broad-spectrum cytotoxic chemotherapy to immune and targeted therapies applicable to multiple systems guided by molecular signatures. Pediatric tumors were approved as one of the first indications among 66.7% ( $n = 18$ ) of the drugs, while supplemental approvals were

<sup>1</sup>Clinical Trial Center, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China. <sup>2</sup>National Central Cancer Registry, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China.

S. Wang, Y. Jiang, and R. Zheng contributed equally to this article.

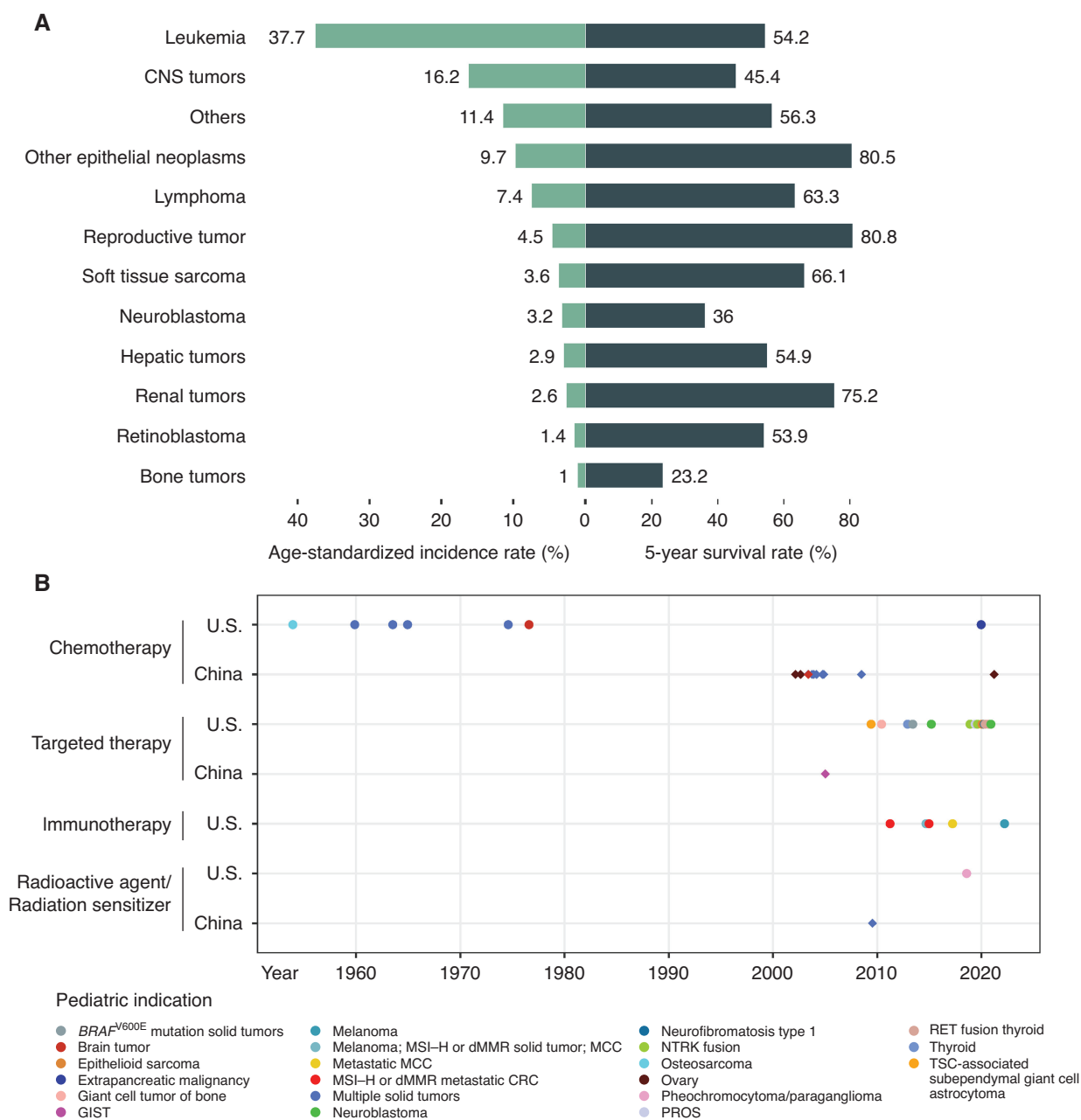
**Corresponding Authors:** Ning Li, National Cancer Center, Cancer Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, State Key Laboratory of Molecular Oncology, Department of Clinical Trial Center, Beijing 100021, China. E-mail: lining@cicams.ac.cn; and Wenqiang Wei, National Central Cancer Registry, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100021, China. E-mail: weiwq@cicams.ac.cn

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**Figure 1.** China bears a heavy burden of pediatric tumors, while restricted therapeutic options exacerbate the problem. **A**, The distribution of incidence and survival rates divided by cancer types during 2014–2018 in China. **B**, Drugs approved for pediatric solid tumors in the United States and China. GIST, gastrointestinal stromal tumor; MCC, Merkel cell carcinoma; CRC, colorectal carcinoma; PROS, PIK3CA-related overgrowth syndrome; TSC, tuberous sclerosis complex.

implemented for the others. The median delay between initial approval for adult indications and the subsequent extrapolation for pediatric cases was 4.3 years (ranging between 0.2 and 9.1 years). Among these drugs, 77.8% were approved via at least one accelerating approach developed by the FDA to expedite drug approval, and 63.0% of these products were recognized as orphan drugs.

In comparison, only 13 drugs have been documented for application in pediatric solid tumors in China (Supplementary Table S3). Eleven of these drugs have a specified dosage for children, whereas the dose in the other two are taken from

adults. Six are included in the FDA approval list with disclosure of pediatric usage, and the other six are universally marketed but lack FDA labels for children. Notably, irisquinone is a radiation sensitizer that was discovered in China.

The overall picture is that far fewer drugs are approved for treating solid tumors in children than in adults, both in China and in the United States. To a degree this is understandable, given that including pediatric subjects in clinical trials for adult-pediatric co-morbidities has remained controversial, and this dearth of data limits our understanding of the proper dosing of pediatric drugs. Yet the gap points

to a significant potential to improve treatment options and outcomes with renewed effort and focused energy.

## CHALLENGES IN RESEARCHING PEDIATRIC SOLID TUMORS

Beyond these social and regulatory factors contributing to decreased approvals for pediatric solid tumors their distinct pathophysiologic features pose additional challenges. Novel therapies mainly arise from two pathways: basic science translation and clinical empirical findings. However, limited biopsies due to clinical practical factors and ethical constraints contribute to limits on data collection for basic exploration, while conservative and prudent clinical practice on children leads to lack of empirical evidence. At present, research on pediatric solid tumors is inadequate and has not attracted sufficient attention.

There are many routes for improving clinical outcomes for pediatric solid tumors, such as advances in imaging techniques, surgical approaches, radiation therapy delivery, and supportive care. Yet, what is most in need are additional specific therapeutic agents and regimens tailored for pediatric patients. Targeted treatments for childhood cancers still rely on drugs originally designed for adulthood cancers. However, only 45% of pediatric cancer driver genes matched those found in adult cancers. Even if a pediatric tumor shares the same target with adults, the efficacy is often quite different. For instance, KRAS mutation is frequent in pediatric hematopoietic cancer and studies have proven that KRAS inhibition shows great efficacy in adult cancer. However, its role in treating children is limited and even when used, the optimal dosage remains unknown.

## PROMISING NEW DIRECTIONS

The ongoing revolution in cancer multi-omics is providing some of the most compelling leads for precision medicine for pediatric solid tumors. For instance, an integrative prospective genetic sequencing study of 309 pediatric cancer patients showed that the overall prevalence of pathogenic or likely pathogenic variants was 10% for patients with hematologic malignancies, but high as 40% to 50% for those with retinoblastoma and other solid tumors (8). It has been estimated that approximately 30% to 67% of pediatric cancers have potentially targetable genetic variants. Most actionable events can be found in the RTK-related, RAS-MAPK, and PI3K-AKT-mTOR signaling pathways (9). The mutation rate of *NF1* is the highest in solid tumors, followed by *PIK3CA*, *PTEN*, and *BRAF*. In comparison with adult cancer, copy number variants (CNV) and structural variants (SV) constitute the majority of events in pediatric cancers, whereas gene mutations are less frequently observed (10). Moreover, pediatric cancers are more likely to be driven by single genes with cancer-type specificity and bear a low tumor mutational burden (TMB).

Although some of these gene alterations or pathological pathways have been widely investigated in adult tumors, their potential in pediatric tumors is poorly understood, encouraging exploring the utility of targeted and immune therapies in these diseases. Novel targeted strategies are also promising in pediatric solid tumors. For instance, adding an monoanti-

body of GD2 to induction chemotherapy can improve early objective responses and yield an encouraging 3-year event-free survival in children with high-risk neuroblastoma (11). Novel cell and genetic therapies, including chimeric antigen receptor (CAR)-T cell, tumor associated antigen (TAA)-based therapies, tumor vaccines, and oncolytic viruses, also deserve investigation although limited evidence has been accumulated for these to date.

## NEW POLICIES IN CHINA AIMED AT ACCELERATING TREATMENTS

With the world's largest population, the goal of China's research and regulatory agencies is to collect the largest and most robust clinical, pathophysiologic, and genetic data for pediatric cancers, overcoming some of the problems encountered in studying rare cancer types. The current status quo certainly argues for an expansion in the development and use of novel therapeutics in children and calls for more investigation on feasible therapeutic targets.

In July 2019, to improve the treatment efficacy of pediatric malignancies, the National Health Community, together with the Ministry of Civil Affairs, National Healthcare Security Administration, the State Administration of Traditional Chinese Medicine, and the State Food and Drug Administration jointly implemented new administrative practices by improving the diagnostic system and guaranteeing medical treatment for children with hematological disorders and malignant tumors. On the basis of the criteria of relatively high incidence, definitive therapeutic effect, and heavy economic burden, a total of 10 diseases were selected as the first batch, including nonneoplastic pediatric hematologic diseases such as aplastic anemia, immune thrombocytopenia, hemophilia, and hemophagocytic syndrome, as well as pediatric tumors such as lymphoma, neuroblastoma, bone and soft tissue sarcoma, hepatoblastoma, nephroblastoma, and retinoblastoma (12). The total number increased to 22 in 2021, with another 12 diseases added to the scope of administration, including CNS tumors (glioma, medulloblastoma, craniopharyngioma, ependymoma), germ cell tumors, head, neck and chest tumors (nasopharyngeal carcinoma, thyroid cancer, pleuropneumoblastoma), neurofibromatosis, Langerhans cell histiocytosis, chronic active EBV infection, immune hemolytic anemia (13). This directive is expected to markedly accelerate advances in the treatment and management of pediatric cancers.

On May 9, 2022, the NPMA issued drafted "Regulations on the Implementation of Chinese Drug Administration Law" (14). The draft comments encourage the research and development of pediatric drugs by guaranteeing priority to the review and approval of new varieties, dosage forms, and specifications of medicines for children. A maximum market-exclusivity period of 12 months will also be provided.

In order to further instruct how to integrate the development of pediatric indications into the overall schedule of drug development, and to protect the rights of children avoiding unnecessary trials, the NMPA issued "Technical Guidelines could for Clinical Development of Pediatric Antitumor Drugs" on March 22, 2023 (15). The guidelines illustrate the development pathways both for adult-child comorbidities and pediatric-

specific tumors, emphasizing that the pediatric antitumor drugs should first conform to the general rules of pediatric drug development, and simultaneously reflect the special considerations for malignant tumors. In general, the development should progress in the order from adult to adolescent to younger children, and the premise of initiating the research in children is obtaining dose with controllable risk and efficacy in adult patients.

For adult-child comorbidities, clinical trials in pediatric populations are generally considered after preliminary data in adults, such as completion of phase II or proof-of-concept trials. After the recommended dose for the adolescent population is clarified, the inclusion of adolescents in the pivotal study of adults is encouraged to minimize the delay in developing the pediatric indication. Otherwise, a separate pivotal study in the pediatric population is usually required. For pediatric-specific tumors, a more aggressive development strategy may be considered. It is recommended to conduct first-in-human trials in adults with other tumors (or in healthy donors), as initial assessment of safety, pharmacokinetics, and pharmacodynamics of the drug. Then modeling simulations in combination with preclinical efficacy data are used to derive safe starting doses for pediatric patients. In principle, randomized controlled trials or single-arm trials are both accepted in the design of pivotal clinical trials.

These steps exemplify the ways in which China is committed to improving cancer management and sharing worldwide the lessons that are learned. By pursuing these objectives, we strive toward the long-term goal in pediatric cancer of helping children become resilient and autonomous adults and having health-related quality of life on par with same age peers.

## Authors' Disclosures

No disclosures were reported.

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## Note

Supplementary data for this article are available at Cancer Discovery Online (<http://cancerdiscovery.aacrjournals.org/>).

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