Research on the development of cancer drugs for children

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Abstract. The development of pediatric cancer drugs is inefficient and must requires a significant development to improve the current situation. According to the research on the development of pediatric cancer drugs, the market condition is analyzed and compared with adult cancer drugs. It is found that even though the drug market for pediatric cancer is significantly smaller than adult cancer’s drug market, it is still important that pediatric cancer drugs are developed in order to better serve the treatment for childhood cancer, and increase the survival rate for malign cancer cases. Through thorough research it also appeared that while the government provides some beneficial programs and insurances for children experiencing pediatric cancer, better insurance plans should be identified. Another important finding throughout research results in the government and legislation area, where the pediatric cancer drugs development process is analysed and has found some potential for the future. As a whole, the effort of the government in both the drug development period and the legislation area with the combination of big pharmaceutical companies’ efforts and the potential creation of new kinds of insurances, the situation for pediatric cancer drugs development can experience a positive change.

1 Introduction

When the problem of cancer is brought up, people are often unfamiliar with the topic, and the childhood cancer group tends to unlikely be taken awareness by the people. With personal experience in a childhood cancer awareness foundation that visits the children’s hospital monthly, it is evident that children going through cancer treatment also need support, and it is noticed that a major problem during children’s treatments is the lack of cancer drugs developed specifically for children. Cancer drugs designed specifically for children are essential to the treatment of childhood cancer because well-developed drugs of this type can give children a better health outcome. However, many children, when treating for cancer, currently have to use a modified amount of adult cancer drugs based on weight. But, due to the differences between children’s bodies and adults’ bodies, using adult cancer drugs as a child could cause future problems like physical harm, psychological effects. Children could be affected physically by having a high level of toxicity left within the body due to the long treatment that could cause serious problems in the future [1]. Furthermore, using adult drugs could also affect children physically, potentially affect organs, tissues, body functions that could hinder the growth and development of the children, and could even have late effects like second cancers. Children using adult cancer drugs could also be affected psychologically. A most obvious effect could be PTSD, because going through the treatment, the child’s experiences could already make them feel stressed, and unable to have a medicine that is designed to treat them directly could make them feel like lacking the social support they need and therefore add on to their anxiety. While cancer continues to threaten the lives of children, there have only been 3 cancer drugs developed specifically for children in the past 40 years, so it is time that we should put more focus on this problem.

Through research, it is found that the development of pediatric cancer drugs is hard but necessary. Researching the current cancer doses, therapies for both the common type of childhood cancer and the rare types, Norris et al found that molecularly targeted anticancer drugs are more effective and have fewer side effects when used to treat childhood cancer [2]. Rodriguez-Nogales et al when researching into the nanomedicines, which is designed to reduce the toxicity of anticancer drugs stated that treatments of pediatric cancer are having a considerable process; however wrong drug does usage are still occurring for children and could eventually cause side effects such as side cardiotoxicity, cutaneous reactions, and many others [3]. It is further suggested that because of many difficulties, the development of necessary pediatric cancer drugs is hindered, so a higher level of partnership between governments and the academic and private sectors must be present. To encounter many of the same difficulties described in the Norris’s research, social and investment strategies have been proposed. Through the analysis of the percent incidences of different cancer cases in different age groups in North America and Europe, Pieters et al revealed that while childhood cancer continues to be a social and economic problem, a consistent national plan for children with cancer is still missing and a key challenge has come to be clinical trial participation with the partnership with families [4]. Further, the social and economic problem of investment

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into childhood cancer research is at a low level with no evidence of increase currently is identified by Loucaides et al [5]. Through a descriptive analysis that review the appropriateness of funding, it is concluded that funding should be more balanced in the area of preclinical research, health systems, and health-care delivery research on methods and mechanisms in the future and researches that the funding was put into should address a wider range of need and minimize wasteful research. Many global and governmental actions have also been brought up when facing the impediments of pediatric cancer drug development. Through looking into the history of childhood cancer treatment and drug development, Adamson et al come to conclude that the development of new agents for treating childhood cancer should be achieved through effective collaboration between the biopharmaceutical industry, global regulatory agencies, academic investigators, and other related people with a necessary improvement in the investment of resources and refinement in the area of legislative effort [6]. Further, through analyzing the policy and legislative change in the US, Europe, Japan, Canada, and Switzerland and their impact on childhood cancer drug research, as well as the analysis of the current collaboration and innovation for pediatric drugs, Bucci-Rechtweg comes to the conclusion that while laws and legislative change are responsible for leading the development of pediatric cancer drugs research and therefore must be present, it can only address a part of the issue [7]. Therefore, a meaningful solution must be a collaboration between all stakeholders within the problems including creating an international database to facilitate data sharing.

The following passages draw a conclusion for the children's cancer drugs market, the insurance related to pediatric cancer drugs, and the legislation for the current pediatric cancer drug development.

### 2 Cancer drugs market for children

Every year, the cases of pediatric cancer account for less than 1% of all cancer cases in the US [8]. It is estimated that in 2021, 10,500 cases of pediatric cancer will be diagnosed, and 5,090 adolescent cancer will be diagnosed, with approximately 1,190 children and 590 adolescents will die from cancer [9]. The most common type of cancer in children are speeded as following:

- **Leukemia**: 38%
- **Brain and Spinal Cord Tumors**: 28%
- **Lymphoma**: 8%
- **Other**: 26%

![Fig. 1. Top Three Common Types of Cancer in Children.](image)

As shown in Figure 1 and Table 1, the most common types of pediatric cancer are leukemia, brain and spinal cord tumor, and lymphoma. While leukemia accounts for most cases of cancer for children, the most common type within it is lymphoid leukemia followed by acute myeloid leukemia. However, while lymphoid leukemia has a high 5-year survival rate of 91% for children, acute myeloid leukemia only has a 5-year survival rate of 68% which in the table above have the least percentage for 5-year survival rate for specific types of cancer.

The incidence rate for pediatric cancer has been increasing about 0.6% each year since 1975 but the reason remains unclear. The death rates for childhood cancer have declined from 6.3 per 100,000 in 1970 to 2.0 per 100,000 [10]. However, most of this improvement is accounted for by leukemia which had a mortality rate of 83% but now has a remission rate of 90% and this is done mostly through optimizing the established chemotherapeutic agents. With cancer being the second leading causes of death of children and number 1 causes of death by disease in children, on average, clinical trials for children begin

### Table 1 Percentage of Cancer Cases and 5-Year Survival Rate of Pediatric and Adolescent Cancer Base on Types of Cancer.

| Types of Cancer | Birth to Age 14 Cases (%) | Age 14 5-Year Survival (%) | Age 15 to Age 19 Cases (%) | 5-Year Survival (%) |
|----------------|---------------------------|---------------------------|----------------------------|---------------------|
| **All ICCC groups combined** | | | | |
| Leukemias, myeloproliferative & myelodysplastic diseases | | | | |
| Lymphoid leukemia | 21 | 91 | 6 | 75 |
| Acute myeloid leukemia | 4 | 68 | 4 | 66 |
| Lymphomas and reticuloendothelial neoplasms | 12 | 93 | 19 | 94 |
| Hodgkin lymphoma (including Burkitt) | 3 | 99 | 12 | 98 |
| Non - Hodgkin lymphoma | 6 | 90 | 7 | 89 |
| Central nervous system neoplasms | 27 | 74 | 21 | 76 |
| Benign/borderline malignant tumors | 8 | 97 | 13 | 98 |
| Neuroblastoma & other peripheral nervous cell tumors | 6 | 81 | <1 | 63 |
| Retinoblastoma | 2 | 96 | <1 | - |
| Nephroblastoma & other nonpituitary renal tumors | 5 | 93 | <1 | - |
| Hepatic tumors | 2 | 80 | <1 | 51.9 |
| Hepatoblastoma | 1 | 83 | <1 | - |
| Malignant bone tumors | 4 | 73 | 5 | 68 |
| Osteosarcoma | 2 | 68 | 3 | 67 |
| Ewing tumor & related bone sarcomas | 1 | 75 | 2 | 58 |
| Rhabdomyosarcoma | 3 | 70 | 1 | 46 |
| Germ cell & gonadal tumors | 3 | 90 | 10 | 93 |
| Thyroid carcinoma | 2 | >99 | 11 | >99 |
| Malignant melanoma | 1 | 96 | 3 | 94 |

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6.5 years after adult trials and the most current standard treatment for pediatric cancer were approved before 1990 with half approved before the mid-1980s. And many of these treatments contain toxic side effects that could cause 2 out of every 3 children survivors to have at least one chronic health condition that could even include second cancers.

### 3 Expense and insurance

The financial burden of many cancer patients is very high due to the high cost of treatment and costs of hospital stays. In a childhood cancer survivor study, adult survivors of pediatric cancer spend a higher proportion of income on out-of-pocket health care costs and have physical problems on paying medical bills. And it is estimated that by 2030, nearly 20% of the U.S. population will be at least age 65 and the total cancer incidence will increase by 45% with approximately more than 400,000 survivors of childhood cancer [11]. Even though the financial burden has appeared as an apparent problem for adult cancer patients and childhood cancer survivors, the cost of care has not been a dominant theme of study due to the relatively small number of instances of pediatric cancer, and the small proportion of health care expenditures by pediatric cancer patients.

Marketplace insurance is a coverage plan for people that are U.S. citizens or nationals and live in the U.S. It is where a child can be added to their parent’s insurance plan when they bought a new plan or on an existing plan in the marketplace. Regulated by the Affordable Care Act, it is required that all marketplace insurance plans to offer child coverage until the child is at the age of 26 disregarding marital status, financial dependency, residency, and many other factors [12]. The government also provides insurance programs for families experiencing cancer. The program Medicare is funded by the federal program provides health coverages for those who are 65+ or those under the age of 65 but have a disability disregarding the family income. The program Medicaid is funded by state and federal program and provides health coverages for low-income families decided through the process based on MAGI methodology which considers the taxable income and tax fillings relationship of the family [13].

While both Medicaid and Medicare consider families as a whole when providing health coverages, the program Children’s Health Insurance Program (CHIP) is designed specifically for children [14]. Being a program that provides low-cost health coverage for all children including those that do not qualify for Medicaid, it is administrated by States and has three possible types: a Medicaid Expansion program, a separate CHIP, or a combination of both types.

### 4 Research and legislation

The pre-clinical drug development for pediatrics usually includes three phases. Phase I is the stages of drug testing usually conducted on adult volunteers. At this stage are rarely involved with the expectation of oncology drugs and surfactant drugs as shown in figure 2 below [15]. Then at Phase II, the goal comes to test for the efficacy and safety of the new drug and is usually conducted on patients. And at this phase, children as test subjects are also uncommon. Then in Phase III, the effectiveness and the role of this new drug is investigated and is tested on children.

The FDA also has pediatric legislation on children’s drug development. The main Pediatric Drug Development Laws include the Pediatric Research Equity Act (PREA), and Best Pharmaceutical for Children Act (BPCA) [16]. The PREA requires a Pediatric Assessment which evaluates the safety and effectiveness of the new drugs for children.
pediatric patients when there is a new indication, dosage form, dosing regimen, route of administration, or new active ingredient. The BPCA provides a financial incentive for voluntary conduct of pediatric studies for individual companies. And the differences between the two include that while the PREA is a mandatory study that only needs required studies for indications under review with having the Orphan indications exempted, the BPCA is voluntary studies that could have expanded indications that might be requested for orphan indications.

When companies are developing a new drug for children, they also need to follow the Pediatric Study Plans (PSP) issued by the Center for Drug Evaluation and Research and the Center for Biologics Evaluation and Research [17]. Companies are required to submit an initial PSP when wanting to submit a market application for a new indication, dosage form, dosing regimen, route of administration, or new active ingredient. An initial PSP should include “(i) an outline of the pediatric study or studies that the sponsor plans to conduct (including, to the extent practicable, study objectives and design, age groups, relevant endpoints, and statistical approach); (ii) any request for a deferral, partial waiver, or waiver . . . if applicable, along with any supporting information; and (iii) other information specified in the regulations.” After the initial PSP is submitted, the FDA will provide comments 90 days after, and the sponsor will need to submit the revised initial PSP 90 days after the comments, and on day 210 the FDA will confirm agreement with the initial PSP.

While the current development phases of pediatric drugs have brought improvement in the past years, innovative clinical trials design also have been created and one that contains potential is pediatric master protocols [18]. As shown in Table 2, master protocols are a clinical trial model that runs continuously and simultaneously evaluates investigational products. It uses a molecular screening approach that combined a number of investigational treatment cohorts that use a molecular screening approach when assigning patients to receive targeted therapy in one of the cohorts decided with the information on their unique tumor profiles and the target of the drug.

Table 2 Design Features of Three Different Pediatric Master Protocol Trials.

| Features | iMATRIXa.gov identifier | Pediatric MATCH | TAPUR |
|----------|-------------------------|----------------|-------|
| Study Types | NCT02541604; NCT02639546 | NCT03155620 | NCT02693535 |
| Eligibility Criteria | Phase 1/2: Dose finding, safety assessing, and activity estimating Children and adolescents (up to 30 y old) with recurrent or refractory solid tumors, brain tumors and lymphomas, with plans to expand to liquid tumors | Phase 2: Dose finding, safety assessing, and activity estimating Children and adolescents (up to 21 y old) with recurrent or refractory solid tumors, non-Hodgkin lymphomas, or histiocytoses with measurable disease | Phase 2: Safety assessing and activity estimating Lymphoma, non-Hodgkin multiple myeloma Advanced solid tumors (proposed amendment to include adolescents [12–18 y old] when scientifically justified) |
| Screening method | Specific to each treatment and based on the mechanism of action of the molecule | Biomarker profiling protocol | Identified genomic variation in patients’ tumors will be matched to drugs on trial. If there is no match, the Molecular Tumor Board can help identify other treatment options |
| Primary study endpoint | Objective response rate | Objective response rate | Objective response rate |
| Treatment assignment | Treatment allocation decisions will be informed by data from completed gate assessments | Computerized algorithm based on levels of evidence for the target and the drugs for the specific target | Agents matched to identified genomic variant in patient tumor |
| Sponsor | Industry | Academic-government | Academic-nonprofit organization |
| Governance Structure | A steering committee that consists of external experts | The NCI-COG Pediatric MATCH Steering Committee consisting of members from NCI, COG, and FDA | United States TAPUR Data and Safety Monitoring Board |

Because the population of pediatric cancer are small, therefore, it is important that studies can use the existing resource effectively while able to have extensive research. All three types of master protocols in the table above includes specific histologically defined tumor type, and have appropriate endpoints and treatment assignment [19].

5 Advice

A possible solution to insufficient pediatric cancer drug development can be helped by having pharmaceutical enterprises continue researching after producing an approved adult cancer drugs on how to create the correspondent cancer drugs for children using the research data they already have from the past research. Having these kinds of companies do continuous research might decrease the cost of researching, and could also have a low marginal cost. Because having produced adult cancer drugs for a specific cancer case means that the company is familiar with the process and has past experiences of the experiences they have already had. Currently, many companies stop continuing researching for children because of the small market and showing apparently that the market forces solely are insufficient to drive a change in the behavior of these companies [20]. Therefore, it is important that government agencies such as the National Cancer Institute (NCI) should play a leading role in the discovery of pediatric cancer drugs through funding extra researches or even possibly taking over the research when needed. While companies and the government can work together to push forward the discovery of pediatric cancer drugs, the FDA should better regulate drugs that will be used for treating childhood cancer to decrease the
The possibility of the occurrence of side effects. And government at the same time should work together with the FDA through actions such as lowering the approval time of new research pediatric cancer drugs, and decreasing the tax revenue for pharmaceutical enterprises when they researched into pediatric cancer drugs to help accelerate the development of cancer drugs.

The cost of treating pediatric cancer drugs is high and could be a burden for families, so another important issue will have insurances to cover the costs of the most common types of childhood cancer. According to a study conducted in Ontario, Canada, during the prediagnosis period, the mean total cost is $1442 [21]. The cost for patients who died within 1 year ($1749) is higher than those who survived ($1083). In the posidiagnosis period, the highest mean net cost for all pediatric cancer cases is leukemia ($157,764) while the mean cost for other childhood cancers is $142,644, and it was also found that the cost of treatment is higher for patients who died within 1 year comparing to others. A compulsory insurance could be created facing the high cost of postdiagnosis period, and should be bought by individuals after they are diagnosed with cancer, and this insurance should cover the mean cost of treating childhood cancer modified basing on the mean cost of treating cancer each year.

6 Conclusion

While the current situation for pediatric cancer drugs have improved a lot in this century and has effectively increased the survival rate of certain kinds of cancer for children, more effort should still be put in. With the increased power in research and technology, more focus should be put into researching for pediatric cancer cases including those that are less common. Through analyzing the market of pediatric cancer drugs, the insurance surrounding pediatric cancer, and the research and legislation for the development of pediatric cancer drugs, the research has been done for the current status of pediatric cancer drugs in the market. It is concluded that through the combination of the government effort and big pharmaceutical companies’ efforts with possible adjustments in the legislation related to pediatric cancer medicines’ development and creation of new kinds of insurances, the current situation can be pushed for a positive change.

References

1. Adamson, Peter C. “Improving the Outcome for Children with Cancer: Development of Targeted New Agents.” CA: A Cancer Journal for Clinicians, vol. 65, no. 3, 2015, pp. 212–220., doi:10.3322/caac.21273.
2. Norris, Robin E., and Peter C. Adamson. “Challenges and Opportunities in Childhood Cancer Drug Development.” Nature Reviews Cancer, vol. 12, no. 11, 11 Nov. 2012, pp. 776–782., doi:10.1038/nrc3370.
3. Garbayo, E., Pascual-Gil, S., Rodriguez-Nogales, C., Saludas, L., Estella-Hermoso de Mendoza, A., & Blanco-Prieto, M. J. (2020). Nanomedicine and drug delivery systems in cancer and regenerative medicine. WIREs Nanomedicine and Nanobiotechnology, 12(5). https://doi.org/10.1002/wnan.1637
4. Pritchard-Jones, Kathy, et al. “Sustaining Innovation and Improvement in the Treatment of Childhood Cancer: Lessons from High-Income Countries.” The Lancet Oncology, vol. 14, no. 3, 20 Feb. 2013, doi:10.1016/s1470-2045(13)70010-x.
5. Loucaides, Eva M, et al. “Global Public and Philanthropic Investment in Childhood Cancer Research: Systematic Analysis of Research Funding, 2008–16.” The Lancet Oncology, vol. 20, no. 12, Dec. 2019, doi:10.1016/s1470-2045(19)30662-x.
6. Adamson, Peter C, et al. “Drug Discovery in Paediatric Oncology: Roadblocks to Progress.” Nature Reviews Clinical Oncology, vol. 11, no. 12, 2014, pp. 732–739., doi:10.1038/nrclinonc.2014.149.
7. Bucci-Rechtweg, Christina. “Enhancing the Pediatric Drug Development Framework to Deliver Better Pediatric Therapies Tomorrow.” Clinical Therapeutics, vol. 39, no. 10, 27 June 2017, pp. 1920–1932., doi:10.1016/j.clinthera.2017.07.043.
8. “Childhood Cancer Statistics: CureSearch.” CureSearch for Children’s Cancer, 25 Nov. 2020, curesearch.org/childhood-cancer-statistics.
9. Siegel, Rebecca L., et al. “Cancer Statistics, 2021.” CA: A Cancer Journal for Clinicians, vol. 71, no. 1, 12 Jan. 2021, pp. 7–33., doi:10.3322/caac.21654.
10. American Cancer Society, Cancer Facts & Figures 2021. Atlanta: American Cancer Society, 2021.
11. Parsons, Susan K., et al. “Cost, Value, and Financial Hardship in Cancer Care: Implications for Pediatric Oncology.” American Society of Clinical Oncology Educational Book, no. 38, 2018, pp. 850–860., doi:10.1200/edebk_200359.
12. Kirchhoff, Anne. Health Insurance Coverage and Medical Financial Burden … unclineberger.org/outcomes/files/2018/10/09182018:_Breakfast_Seminar_Kirchhoff.pdf.
13. “Eligibility.” Medicaid, www.medicaid.gov/medicaid/eligibility/index.html.
14. “Children’s Health Insurance Program (CHIP).” Medicaid, www.medicaid.gov/chip/index.ht ml.
15. Rieder, Michael, and Daniel Hawcett. “Design and Conduct of Early Phase Drug Studies in Children: Challenges and Opportunities.” British Journal of Clinical Pharmacology, vol. 82, no. 5, 2016, pp. 1308–1314., doi:10.1111/bcp.13058.
16. McCune, Susan. “FDA Overview of the Pediatric Legislation.” FDA, 21 Nov. 2019, www.fda.gov/media/132890/download.
17. Center for Drug Evaluation and Research. “Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Initial Pediatric Study Plans Guidance for Industry.” U.S. Food and Drug Administration, FDA, July 2020, www.fda.gov/regulatory-information/search-fda-guidance-documents/pediatric-study-plans-content-
and-process-submitting-initial-pediatric-study-plans-and-amended.

18. “FDA-University of Maryland CERSI Pediatric Master Protocols Workshop.” U.S. Food and Drug Administration, 23 Sept. 2016, www.fda.gov/science-research/advancing-regulatory-science/pediatric-master-protocols#:~:text=Master%20protocols%20that%20run%20continuousl y, focused%20on%20pediatric%20master%20protoco ls.

19. Khan, Tahira, et al. “Accelerating Pediatric Cancer Drug Development: Challenges and Opportunities for Pediatric Master Protocols.” Therapeutic Innovation & Regulatory Science, vol. 53, no. 2, 2018, pp. 270–278., doi:10.1177/2168479018774533.

20. Kantarjian, Hagop, and Leonard Zwelling. “Cancer Drug Prices and the Free-Market Forces.” Cancer, vol. 119, no. 22, 26 Aug. 2013, pp. 3903–3905., doi:10.1002/cncr.28330.

21. De Oliveira, Claire, et al. “Costs for Childhood and Adolescent Cancer, 90 Days Prediagnosis and 1 Year Postdiagnosis: A Population-Based Study in Ontario, Canada.” Value in Health, vol. 20, no. 3, Mar. 2017, pp. 345–356., doi:10.1016/j.jval.2016.10.010.