LEUKEMIA & LYMPHOMA SOCIETY®

Pediatric Blood Cancer Research Inititative

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May 2018

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1. Executive Summary

Pediatric blood cancers (ages 0-19) include primarily acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), Hodgkin's lymphoma (HL) and non-Hodgkin's lymphoma (NHL). Collectively, they comprise 40% of all pediatric cancers, with ALL as the most common childhood cancer (approximately 3200 new cases/yr in the US or 20% of all pediatric cancers). While the survival rates for childhood ALL, HL and NHL have dramatically improved in the past 50 years, and indeed cure rates for some of these types of cancer exceed 80%, only 50% of pediatric AML patients survive 5 years or longer.

Improvements in childhood ALL have occurred by continually improved use of cytotoxic agent combinations, many of which were initially developed in the 1950-1970's, as well as improvements in hematopoietic stem cell transplant (HSCT) technology. In fact, in the past 20 years, the FDA has only approved **ONE** new therapy exclusively for pediatric blood cancer patients (Tisangenlecleucel). Resistance is common and for some children or adolescents many therapies simply do not work resulting in the use of multiple rounds of alternative chemotherapeutic drugs to treat refractory or resistant disease. To improve treatment for children cancer patients, it is no longer sufficient to just to optimize the current regimens. New drugs are needed to improve the outcome.

Beyond the control or eradication of some of the pediatric blood cancers, there is a significant price to pay for the curative therapies currently in use. Pediatric blood cancer patients are at substantial risk of developing subsequent blood cancers as well as solid tumors, many of which can manifest years after completion of therapy. In addition, pediatric patients develop cardiovascular, pulmonary, and other end-organ deficiencies that are correlated with early death. Children in particular have many organs that are not fully developed (i.e. skeleton, brain) and therefore, can sustain permanent impairment. This can lead to chronic conditions that significantly impact quality of life.

The LLS goals for future of research for pediatric blood cancers, based on experts' recommendations and LLS internal discussion, are four-fold:

1. Understand the molecular basis of these diseases, especially the defects that are unique to pediatric patients.
2. Develop as effective, or more effective targeted therapies or immunotherapies that have long-term safety profiles devoid of toxicities compared to current cytotoxic chemotherapy.
3. Develop better predictive methods to identify those patients who need intensive therapy (i.e. high risk patients) as well as identify those patients at high risk for secondary complications due to therapy. The same approach would identify patients who do not need intensive therapy and therefore avoid unwanted side effects.
4. Implement primary and secondary prevention strategies to detect and reduce late effects.

LLS' expansion for pediatric research calls for an increase of approximately $10 M over five years. This includes funding for one $5 M, 5-year collaborative research program, as well as at least four $0.6 M translational research projects, which will activate in 2019.

On September 7, 2016, the Blue Ribbon Panel presented its report to the National Cancer Advisory Board. The report describes 10 transformative research recommendations for achieving the Cancer Moonshot's ambitious goal of making a decade's worth of progress in cancer prevention, diagnosis, and treatment in just 5 years. One of the 10 recommendations is about how to intensify research on the major drivers of childhood cancers. With today's technologies, coordinated efforts involving the government, non-profit sector, academics, and private sectors, there is every reason to believe that the treatment for pediatric blood cancer patients will improve dramatically.

2. Background

2.1. Pediatric blood cancer statistics

Cancer is the leading cause of death of children (age 1-19) in the United States (1). Although total amount of new cases of leukemia and lymphoma cancers in this age bracket is small, about 10% of all ages with cancers (Fig. 1), pediatric blood cancers including leukemia and lymphoma (ages 0-19) represent about half of all pediatric cancer (Fig.1), underscoring a unique health issue for children.

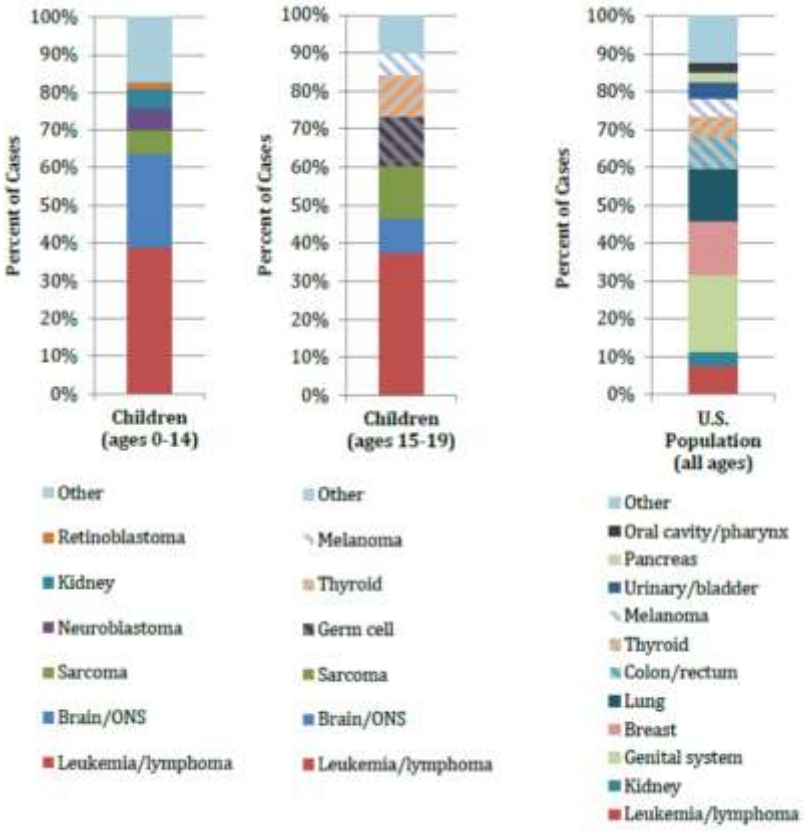


Fig. 1. The distribution of cancers within the US populations. Sources: Proportions for "Children (ages 0-14)" and US Population (all ages)" are based on estimated cases in the US for 2013. American Cancer Society. Cancer Facts & Figures 2013. Proportions for "Children (ages 15-19)" are based on the reported US cases for 2006-2010 from NCI's Surveillance, Epidemiology, and End Results Program

Note: While this report is limited to children with hematological malignancies, these cancers also occur in adolescent and young adults (AYA), defined as a range of 15-39 years of age and is about 15% of all cancers (2). While the efforts for LLS in pediatrics may expand to AYAs, the molecular basis of the disease are distinct and the therapeutic outcomes are worse for this age range compared to children (2). Therefore, distinct research plans are likely to be needed for AYAs and are beyond the scope of this report.

2.2. The incident rate and estimated new cases for 2016

The incidence of pediatric blood cancer has increased with the exception of Hodgkin Lymphoma (HL) since 1975 (Fig. 2). In particular, ALL incidence shows the highest increase. The factors affecting the increase in incidences of these cancers remain unclear.

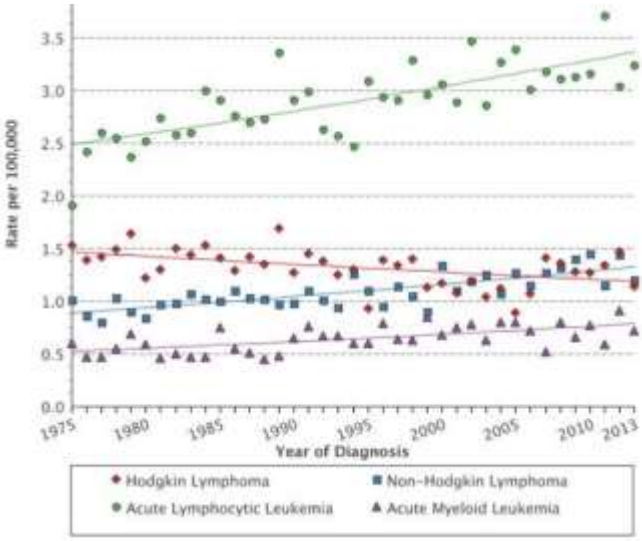


Fig. 2. Incident of pediatric blood cancers since 1975. Source: National Cancer Institute. "Surveillance epidemiology and End Results [SEER] Program: Fast Stats." Available at http://seer.cancer.gov//faststats/index.php

In 2016, the estimated new cases for major pediatric blood cancers was about 7,000 as shown in Fig.3. ALL is obviously the most common types of pediatric blood cancer, which represents 50% of all pediatric blood cancer cases and 75% of childhood leukemia cases (3), leading the others with 1057 for AML, 1161 for NHL, 1071 for HL, 181 for CML, 19 for CLL. Among NHLs, Burkitt's lymphoma (BL) and diffuse large B-cell lymphoma (DLBCL) are the most common subtypes (4).

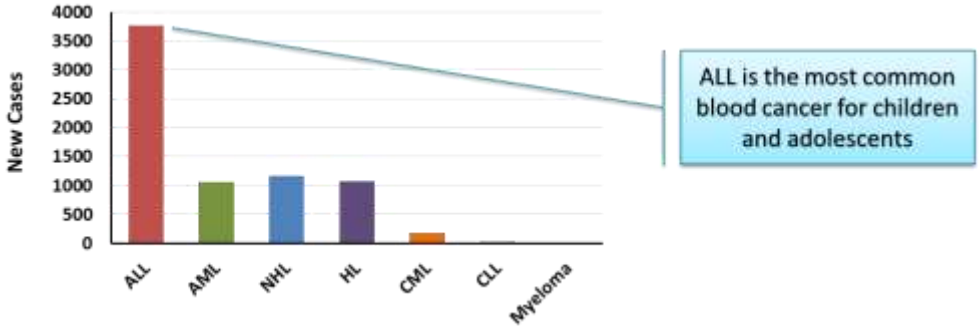
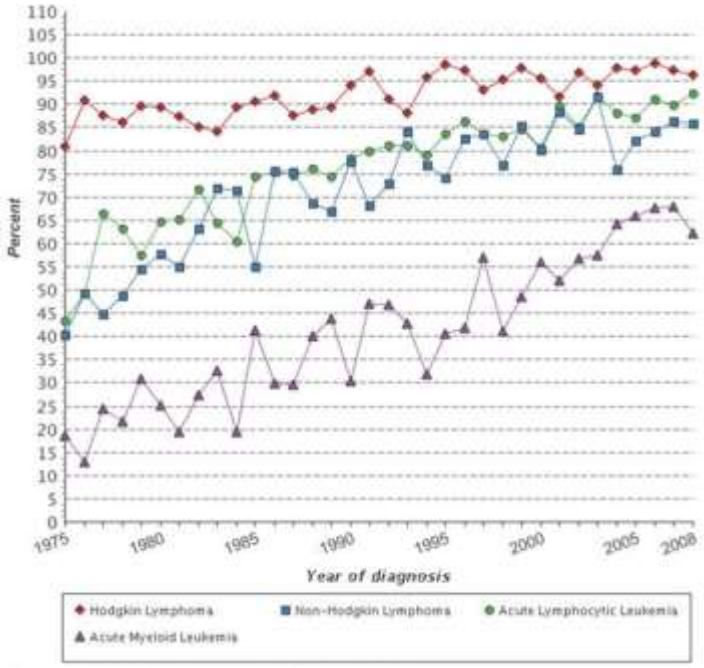


Fig. 3. Estimated new cases of pediatric blood cancer in 2016. The estimated numbers are based on SEER source. Available at http://seer.cancer.gov//faststats/index.php

2.3. 5-year survival and beyond

Outcomes for children continue to improve for most types of cancer (data not shown). Survival for the major pediatric blood cancers has also increased steadily since 1970s (Fig. 4a). The improvements in survival of childhood ALL have been most dramatic based on the optimization of use of a combination of cytotoxic agents and stem cell transplantation (Fig. 4b).

a.



b.

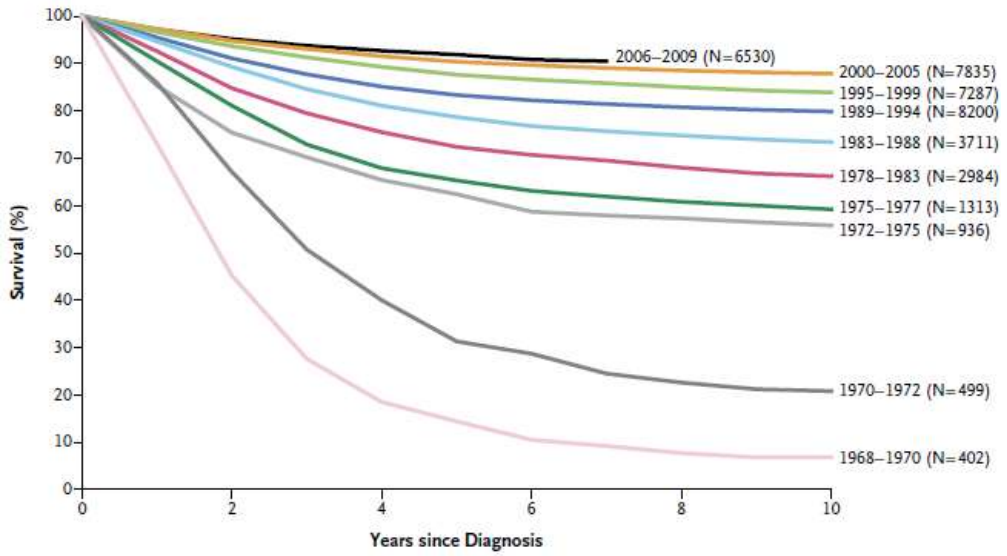


Fig. 4a Survival of pediatric blood cancers. Source: National Cancer Institute. "Surveillance epidemiology and End Results [SEER] Program: Fast Stats." Available at http://seer.cancer.gov//faststats/index.php.

Fig. 4b. 10-year survival for ALL based on children with ALL who were enrolled in COGs clinical trials from 1968-2009 (5).

However, it is perhaps worth noting that the increase in survival has been in part due to changes of regime and schedule of using old cytotoxic drugs, and there is a lack of new treatments to fundamentally change the outlook of ALL. It is also important to note that there is a great deal of variation in prognosis depending on subtypes and stages in cancers with even high survival rates.

Figure 5. shows the survival rates after relapse in ALL patients who received frontline therapy on COG trials conducted between 1988-2002 (6). Of 9585 enrolled on these studies, survival after relapse was determined in 1874 extramedullary and marrow relapses. The survival curves are separated according to timing of relapse (red = early) and also according to trial era with triangles representing relapses after treatment on earlier generation trials in the later 1980s to early 1990s, and the circles representing more recent trials from the late 1990s to early 2000s. Outcomes were similar irrespective of trial era, and show survival rates after late relapse are ~50%. The outcomes are far inferior for those with earlier relapses, with about 23% survival rates in patients who relapsed between 18 to 36 month and only 10% for those who relapse within 18 months.

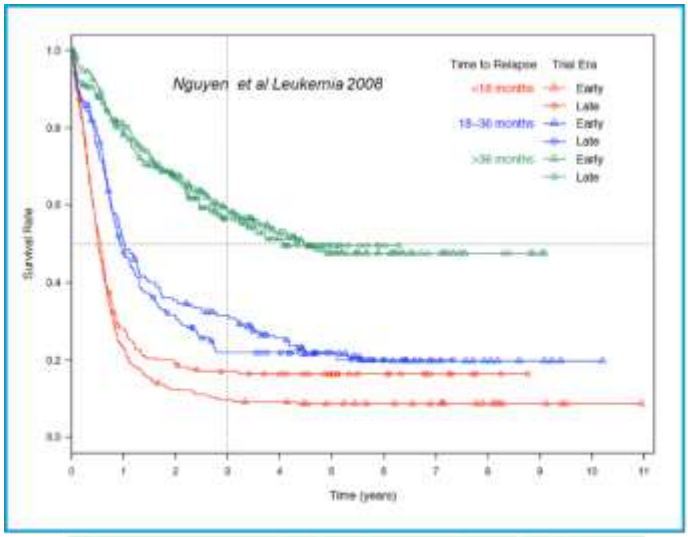


Fig. 5. Survival after bone marrow transplant.

Furthermore, although 5-year event free survival improves with decrease in minimal residual disease (MRD) (Fig. 6), showing 88% EFS probability, many relapses can still occur unpredictably. The failure rate is as high as 51% for those relapsed young ALL patients due to ineffective treatment (7).

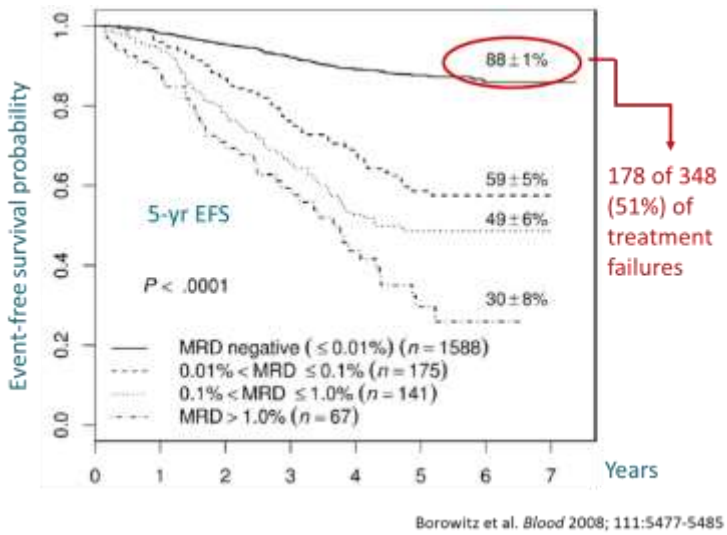


Fig. 6. Event free survival probability based on minimal residue disease measurement.

2.4. Mortality (2016)

Over the past 40 years, the mortality rate for all pediatric cancers, including major blood cancers, has continued to decline with the exception of AML. For example, the pediatric blood cancer with the highest mortality used to be ALL, which has fallen dramatically since 1975 (Fig. 7). The decrease in mortality may in part be attributed to the fact that majority of the pediatric blood cancer patients were enrolled in clinical trials. However, these encouraging statistics do not tell the whole story. While 5-year survival in pediatric ALL has increased steadily over the years, certain subtypes of ALL have no adequate cures. Strikingly, over the past 40 years, there has been only two new treatments to change the outcome as previously indicated (section 2.3.; Fig. 4).

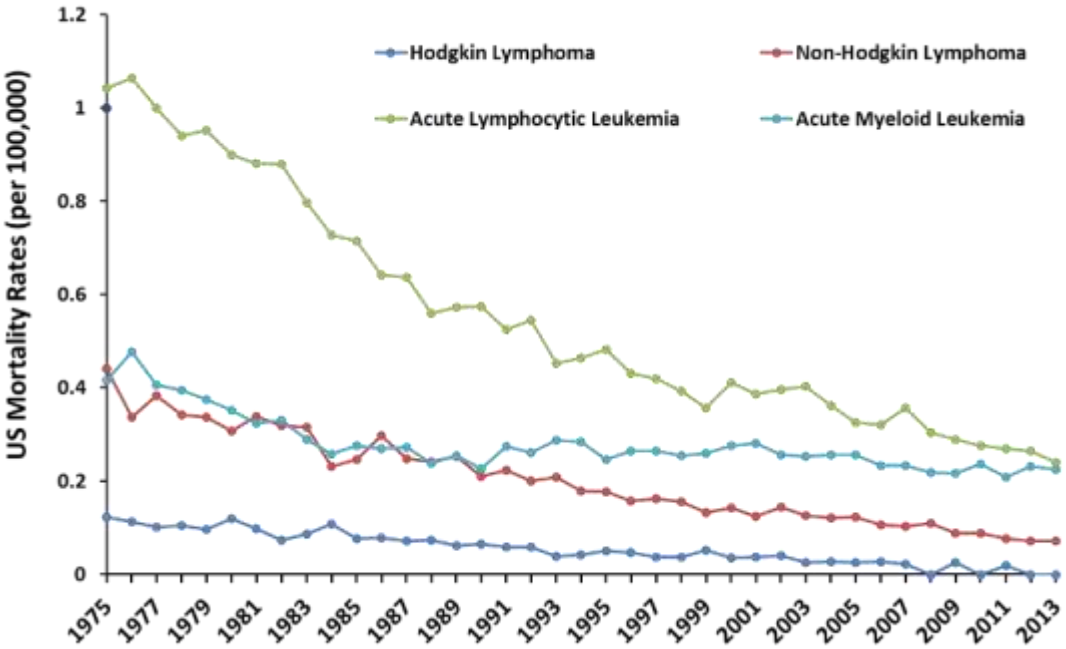


Fig. 7. US mortality rates (per 100,000) for pediatric hematological malignancies. Source: National Cancer Institute. "Surveillance epidemiology and End Results [SEER] Program: Fast Stats." Available at http://seer.cancer.gov//faststats/index.php

Compared with ALL, the outlook for pediatric AML patients is far worse. Even though pediatric AML cases are far fewer than pediatric ALL, the mortality rate is about the same (Fig. 8), clearly illustrating that AML is a devastating disease and the need for continuing research to identify effective treatments for these children. Beyond that, despite increases in survival, the pediatric patients face life-long health issues, including serious chronic conditions and secondary cancers. Quality of life becomes an outstanding issue for these young patients, if the year of lost is considered (an estimate of the average years a person would have lived if he or she had not died prematurely).

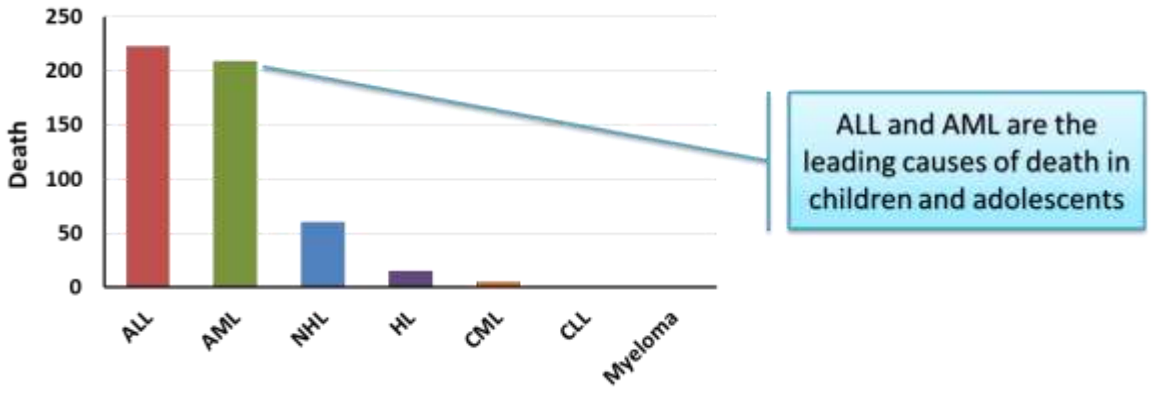


Fig. 8. Estimated death of pediatric blood cancers in 2016. The estimated numbers are based on SEER source. Available at http://seer.cancer.gov//faststats/index.php

2.5. Late effect and long-term survivorship

While we have observed a steady decline in mortality and increase in survivorship over the years, an emerging issue is the growing number of long-term survivors who have to endure the side effects related to the treatment. It is estimated that there are nearly 500,000 pediatric cancer survivors in the US (Fig 9). What is disconcerting for children in particular is that the recurrence plus secondary diseases that eventually catch up years later. It was estimated that nearly 40% of childhood cancer survivors aged 35 or older have experienced a severe or life-threatening health condition, or have died, which is a rate over five times higher than that of their siblings (8). Figure 10 shows that mortalities unrelated to original cancer increases dramatically after 40 to 50 years. The observed cumulative death from all causes other than recurrence reached about 19% at 50 years after initial diagnosis while only 6% was expected from the general normal populations. The data suggest that many survivors will encounter health issues many years after their first cancer diagnosis and benefit from improved treatment with fewer long-term effects or intervention therapies that can mitigate the likelihood of additional diseases.

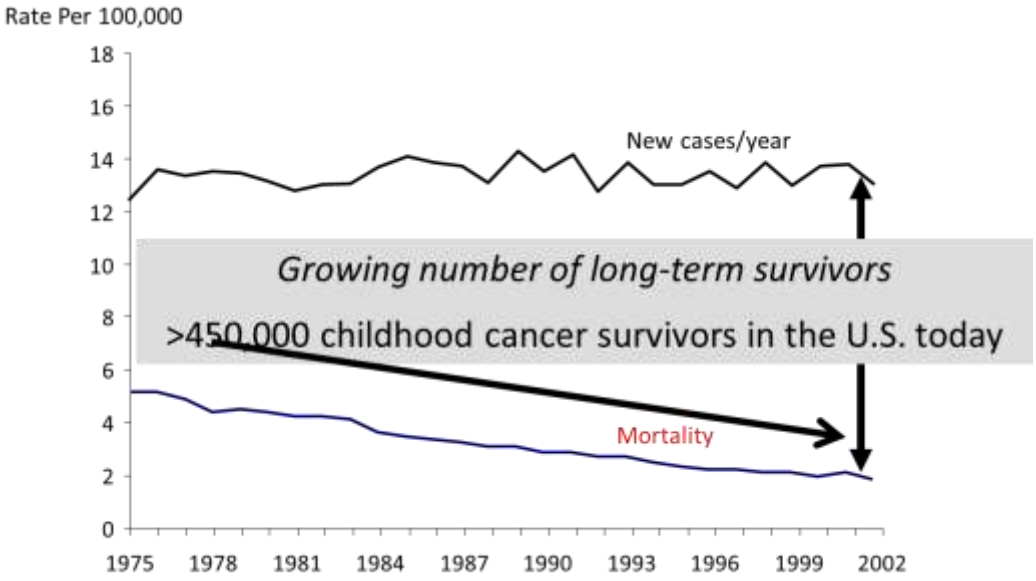


Fig. 9. Mortality and survivorships. Source: Seer, 1975-2002, Division of Cancer Control and Population Sciences, NCI, 2005. Age-adjusted to the 2000 Standard population.

Among the most serious complication is cardiovascular disease mediated by the use of anthracyclines, which are commonly used in the treatment of ALL, AML and HL. Not only is heart failure, coronary artery disease and cerebrovascular accident 15, 10 and 9-times as likely to occur in survivors of childhood cancer compared to their siblings (9), respectively, but the increased risk of cardiovascular disease persists at least 45 years after treatment (10) and once diagnosed with congestive heart failure, the 5 year survival rate in children is <50% (11). The incidence of cardiovascular disease is correlated with the anthracycline dose, and increases dramatically once the dose exceeds cumulative exposure of 250

mg/m2, which is close to or below the typical exposure of anthracyclines used in protocols to treat ALL, AML or HL (12) (Figure 10b). The increased incidence of cardiovascular disease is also apparent after radiation or anthracycline-based therapy for Hodgkin's lymphoma, based on analysis of patients up to 40 years after treatment (13).

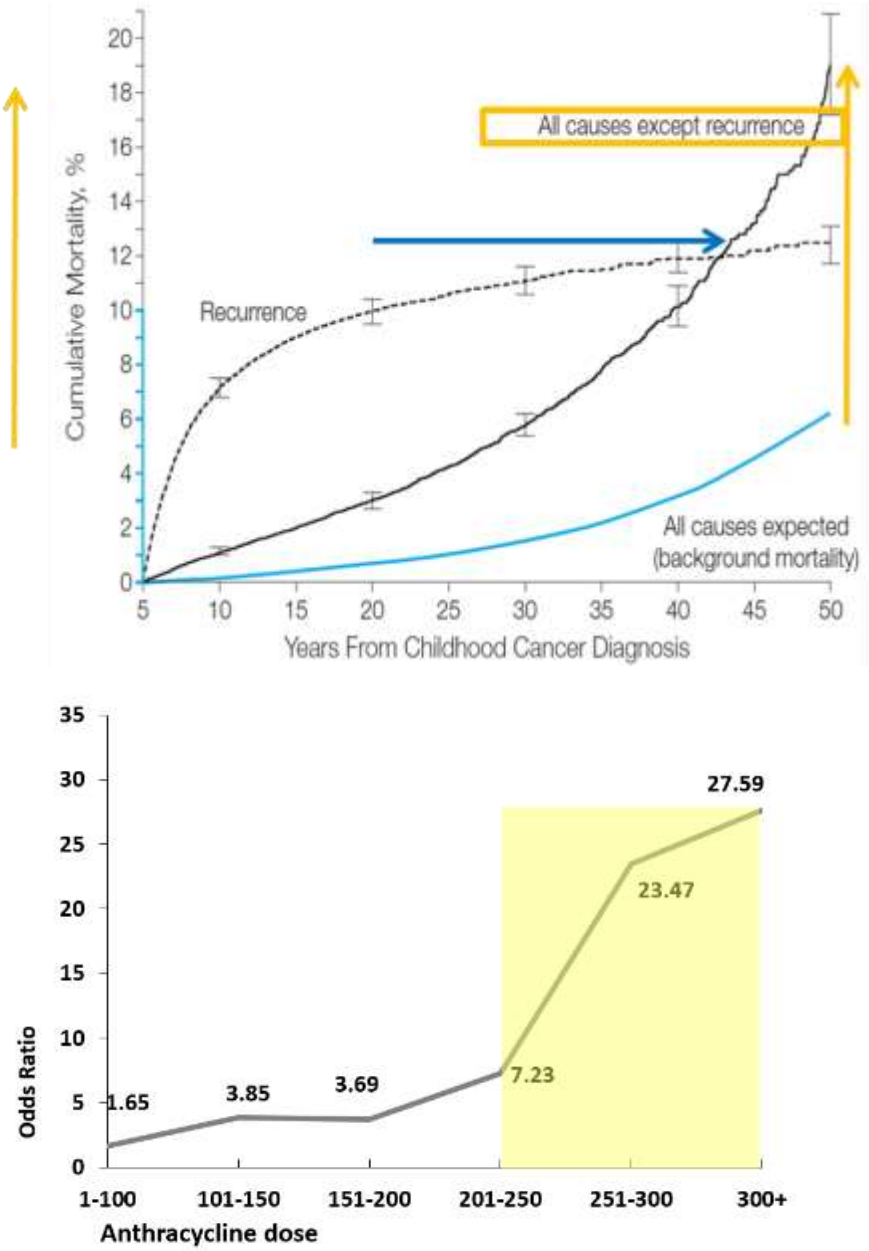


Fig. 10. Mortality unrelated to the original cancers over the years. A. Observed cumulative mortality of all causes of death other than recurrence was 19.0% at 50 years from initial diagnosis, whereas 6.3% was expected based on rates from the general population (6). B. Risk of cardiovascular disease based on cumulative exposure to anthracyclines (from S. Bhatia, with permission).

2.6 Approved targeted therapies in pediatric hematological cancers

Although progress has been meager in developing new therapies for pediatric blood cancers, there are some notable advances particularly for the treatment of ALL and CML. (There are no targeted therapies approved for childhood AML and therefore treatment relies on standard anthracycline plus cytarabine combination therapy coupled with stem cell transplantation).

Erwinase. A new form of asparaginase derived from *Erwinia chrysanthemi*, known as Erwinase, was approved by the FDA in 2011 to treat ALL in patients with hypersensitivity to E-coli-derived asparaginase (Pegaspargase), which is the standard of care for the disease. Erwinase is used in a multi-agent, cytotoxic regimen.

Imatinib, Dasatinib and Nilotinib. These oral medications are approved for use in pediatric patients with Philadelphia+ CML in chronic phase who are newly diagnosed or have recurrent disease after stem cell transplant. Imatinib, dasatinib, and nilotinib were approved for childhood CML by the FDA in September 2006, November 2017, and March 2018, respectively. These agents improve survival in Ph+ ALL compared to Ph- ALL (e.g. 14, 15) and are likely to have utility in Ph+ like ALL (16), but are not FDA approved.

Blinatumomab. This intravenous bispecific CD19-directed CD3 T-cell engager is approved for the treatment of Philadelphia chromosome-negative recurrent ALL in patients of all ages. Based on a phase I/II trial with 70 pediatric patients, 39% of the patients obtained a complete remission within the first two cycles of blinatumomab, with a median overall survival time of 7.5 months (17). Cytokine release syndrome and neurological toxicities were found. Blinatumomab was approved by the FDA in December 2014. The label was expanded on March 29, 2018 to include approval for the use of blinatumumab in adults and children with B-cell ALL who are in remission but have still not achieved MRD.

Tisagenlecleucel. Kymriah is a CD19-directed genetically modified autologous T-cell immunotherapy for the treatment of patients up to 25 years of age who have B-cell precursor ALL that is refractory or in second or later relapse. As recently reported in the registrational trial (Eliana), in the 75-patient study the overall response rate was approximately 80% (60% CR and 21% CRi) with a 6-month overall survival of 76%. In addition, the median duration of remission in 61 patients that achieved a CR or CRi, was approximately 60% at 20 months (18). Cytokine release syndrome and neurological toxicities were found. Kymriah was approved by the FDA in October 2017.

3. The Challenges

3.1. Children are different from adults

3.1.1. Differences in biology

Although both children and adult suffer from the same types of cancers, the biological and clinical characteristics of nearly all childhood cancers differ substantially from adult cancer (19, 20). Two large studies examining over 1000 pediatric patients from 24 tumor types (21) or 1700 patients over 6 tumor types (22) found that, using exome and transcriptome analyses, pediatric tumors are less mutated than adults, frequently had a single driver mutation, and that germline mutations were more frequent in pediatric tumors. Beyond that, approved or experimental targeted therapeutics already exist to about 50% of the mutations reported in pediatric cancers. In particular, it is now well established that pediatric and adult B-cell leukemias and lymphomas have different genomic profiles (23-25) (Fig 11, right). The Ph-positive or Ph-like ALL phenotype is prevalent in childhood ALL and present actionable targets (with BCR-ABL kinase inhibitors) (28). Other actionable targets have also been identified (Fig 11, left).

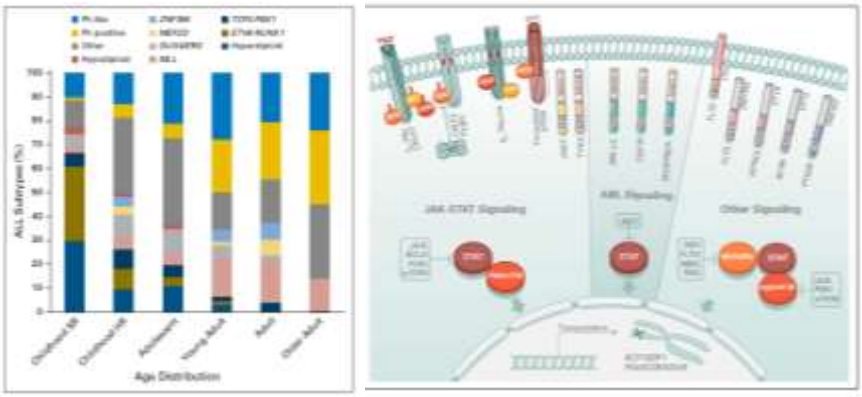


Figure 11. Age distribution of ALL subtypes and actionable targets. From reference 16.

ALL can have a distinctly different prognosis at different ages, partly due to different genetic subsets that tend to occur as a child develops. Beyond DNA mutations, recent studies suggest that epigenetic changes are found at comparatively high rates in pediatric cancers compared to adult cancers. For example, one study found that over 50% of pediatric high-grade gliomas, osteosarcomas, and T-cell ALL tumors harbor epigenetic mutations (24). The mutational analysis of 264 cases of pediatric and young adult T-ALL was recently reported (25). Noncoding genomic alterations for childhood cancers are under explored. The elucidation of unique biology at molecular level provides hope for developing better and less toxic precision medicine for children. For example, chromosomal rearrangements of the mixed-lineage leukemia gene (MLL) is predominantly expressed in childhood leukemia (26, 27). LLS has

supported multiple projects through research grants and TAP to identify drugs to inhibit MLL rearrangements-initiated effects.

Like childhood ALL, childhood AML is molecularly distinct from adult AML. Based on a dataset of 1021 AML cases, the mutational rates of certain genes is childhood AML have a markedly different frequency compared to adult AML (Fig 12).

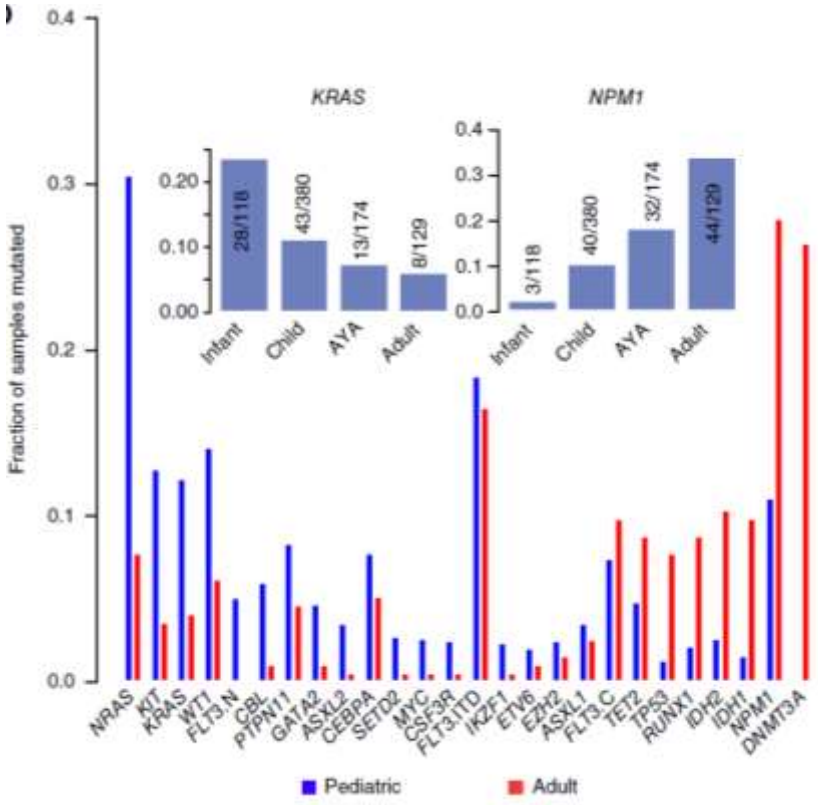


Figure 12. Comparison of mutational frequency of selected genes in pediatric vs. adult AML (see 28).

For example, as recently reported by Bolouri et al (28), the incidence of FLT3-ITD, RAS, and IDH mutations is similar, 4-times more common, and more than 5-times less common in childhood AML vs. adult AML, respectively. As there are FDA approved therapeutics that target FLT3 and IDH mutations (approved for adult AML), this has immediate therapeutic implications. In addition, transcription profiles and some gene fusions are considerably more prevalent in children compared to adults with AML (e.g. 23). Most notably, mesothelin is express in 30% of childhood AML and much lower, less frequent expression in seen in in adult AML (29).

3.1.2 Differences in response to the same drugs

Due to the lack of data on safety, efficacy, and dosage in children, physicians have commonly resorted to off-label use of therapies evaluated in, and labeled for, adults. However, children are not just simply small adults. When applied to children, the results may differ in side effects and efficacy due to differences in pathophysiology, diseases variants, pharmacodynamics, and immune response. Not only conventional therapeutics but also current targeted therapies that are approved can have different side effects in children than in adults, including immunosuppression and impaired sperm production (30). As new cancer therapies continue to evolve, there is an urgency to understand differences in response and long-term adverse effects on children. We need to remain vigilant due to unique adverse effect profiles in developing children. Particularly in children, the undesirable general adverse effects are manifested long-term in the form of short stature, impaired fertility, cardiac dysfunction, and neurocognitive deficits after therapy is discontinued (9).

3.2. Sample size too small

Pediatric blood cancer patients are relatively few compared to that of other cancers such as lung, prostate, and breast. Therefore, there is a limit to the availability of patient cohorts as well as the biological samples. The rarity makes it difficult for researchers to gather sufficient number of samples to interrogate the diseases and develop treatment strategies. In order to enhance collaborative efforts for tissue collection and information sharing, the Pediatric Cancer Genome Project was launched in 2012 (St. Jude and Washington University). Subsequently, NCI launched the TARGET (Therapeutically Applicable Research to Generate Effective Treatments) Project with the goal to advance scientific discovery in childhood cancers and foster collaboration in both the public and private sectors to hopefully speed up discoveries related to childhood cancers, including AML and ALL. In addition, Foundation Medicine has recently reported on the genomic profile of >1000 pediatric cancers (31).

Through the TARGET initiative, important drug targets and potential therapeutic intervention for pediatric cancer have been identified. Key signaling pathways associated with high-risk ALL have been found. One of these is the JAK signaling pathway that can be targeted with an FDA-approved small molecule inhibitor, ruxolitinib. Moreover, the TARGET ALL team led by Dr. Charles Mullighan established the molecular profile of Philadelphia chromosome-like ALL and lays the important foundation for new treatments for these patients with specific molecular profiles (32). In addition, ETV6-RUNX1 fusions are much more prevalent in children compared to the AYA or adult ALL population. Finally, Dr. Meshinchi's recent study showed that mesothelin is a target primarily expressed in pediatric AML; he proposes to use an mesothelin- antibody conjugate developed by Bayer (initially as a therapy for adult kidney cancer) to treat pediatric AML patients (29).

It is important to understand that although all of these projects have done extensive analyses, there is more work to be performed to understand the genetic information. In particular, more samples need to be analyzed using a multi "omic" approach.

3.3. Late effects

As stated above, 40% of childhood cancer survivors aged 35 or older have experienced a severe or life-threatening condition, or have died (5 times higher than seen in the siblings of these survivors who were not treated for cancer). As new therapies are developed, the long-term consequence of the therapy will need to be evaluated. However, it is difficult to predict or study the long-term effects of targeted therapies in children due to the newness of these therapies and the small number of children to whom they may apply.

There is an urgent need to carry out biomarker studies that will allow reasonable prediction of potential late effects. For example, Troponin-T has been studied as a predictive marker of cardiac risk in pediatric ALL patients (33, 34). More studies such as this are needed for cytotoxic chemotherapy and radiation treatments that typically kill or inhibit cancer cells as well as normal cells. Even targeted therapy may affect normal cells as well and have a long-term effects (30).

The long-term effects of therapies that activate the immune system are just beginning to be evaluated. In preliminary studies, the long-term consequences of immunocheckpoint inhibition in patients with blood cancer (who in some cases may require a subsequent transplant) suggest that there may be long-lasting immune alterations (35). In addition, the effects of long-term B-cell depletion mediated by CD19- CAR T therapy (for the treatment of childhood ALL) remains to be fully determined, although this clearly needs to be examined, since genetically engineered T-cells given to patients with ALL can persist for more than 1.5 years (36), and certain CAR T cells have an estimated half-life of at least 17 years (37).

3.4. Lack of pediatric drug discovery

In order to overcome the above mentioned challenges, the ultimate solutions are more effective and better medicine. However, most of the cancer drugs were developed first in adult patients and then found effective in children. It is rather remarkable that from 2000-2018, only three therapies (CD19-CART, Erwinase, and Blinatumomab) out of >50 approved new cancer therapies were developed initially for children's blood cancer (for ALL). Moreover, only an additional 3 drugs (imatinib, dasatinib, nilotinib) were approved for childhood leukemias during this period. Strikingly, there are no new drugs approved for pediatric AML. Given the available cutting-edge technologies and molecular knowledge of the diseases, it seems plausible that better and more effective drugs should have been developed. The reasons for the lack of specific pediatric cancer drug discovery are several fold.

3.4.1. Inadequate funding for pediatric blood cancer research

3.4.1.1. Decline in government (NCI) funding

NCI is the largest single government source of childhood cancer research. NCI's role in supporting research and infrastructures is well known, but it lacks the resources to support late stages of drug discovery and development. NCI funding for Childhood cancer remains about the same in the past 5 years (Table 1). However, when inflation is considered, the total funding from 2004-2015 has declined by 24% for pediatric cancers (and parallels the reduction in NIH funding overall). NCI funding for Children's Oncology Group also declined by 30% from about 30 M (2004) to 20 M (2015). Moreover, NCI funding specifically for leukemia and lymphoma is also flat and slightly down when inflation is considered (Table 1). Tightened budgets have forced investigators to spend too much time seeking funding instead of conducting actual research.

Table 1. NCI funding for pediatric cancer over 5 year period has been flat. Source: NCI Funded Research Portfolio: http://funderresearch.cancer.gov/nciportfolio.

Year	Overall childhood cancer funding (millions)	Funding to Leukemia/Lymphoma (millions)	Adjusted funding to Leukemia/Lymphoma (millions)
2010	197.1	56.1	56.1
2011	195.5	39.3	38.1
2012	208.1	58.5	55.6
2013	185.1	57.0	53.4
2014	203.7	55.3	50.9

3.4.1.2. Lack of incentives for industries to develop pediatric cancer drugs

Pharmaceutical industries' interest in pediatric cancer research is affected by economic evaluations. Because of the rarity of blood cancer cases, the marketplace for new drug development is simply too small and not profitable for the drug companies to consider development of new therapeutics. Even with promising therapeutics that are being tested in adult cancers, drug companies are usually reluctant to launch trials in children for fear that if unfavorable results are observed early in the FDA approval process, it will delay approval and thus negatively impact on potential profits. Beyond this, newly approved pediatric drugs require long-term follow up (decades), as is the case for CAR T therapy for childhood ALL. Clearly, this increases the cost for pediatric drug development.

To mitigate these limitation, polices or rules need to be implemented in order to provide incentives to drug developers to commit to pediatric cancer development. It is unlikely that charging a higher price will be an achievable

option. In light of these considerations, a few policies have been implemented. For example, Pediatric Exclusivity allows a company to obtain an additional 6 month of exclusivity after approval. Creating Hope Act (2011) provides voucher to pediatric drug developer with rights to FDA priority review for any other drug or biologic, including a large market adult drug or biologic that would otherwise receive standard review. As a further incentive, these rights may be sold from one pharmaceutical company to another. This act has been extended to 2020. In addition, the Research to Accelerate Cures and Equity (RACE) for Children Act was passed by Congress in August 2017. This law stipulates that pharmaceutical companies must submit a pediatric development plan to the FDA for molecular targeted new therapeutics after the completion of phase II studies (in adults). FDA must approve this plan (or ask for revisions). The law goes into effect in August 2020 and FDA is tasked with defining a list of molecularly targeted agents prior to enforcement of the new law.

Nevertheless, even with these incentives commercial companies are still reluctant to invest in pediatric drugs and indeed, can request deferrals to delay further exploration of new therapies in children. New policies and additional incentives like reduction in rebate to Medicaid will have to be considered in order to encourage pharmaceutical companies to expedite pediatric drug discovery and development efforts. Beyond this, experimental evidence, both in vitro and in vivo (using valid tumor models) should greatly help justify further pediatric development.

3.4.1.3. Non-profit and philanthropy

Non-profit and philanthropy are other major sources that support pediatric blood cancer research. Some non-profit organizations have even taken the responsibility to develop drugs themselves (e.g. The Cystic Fibrosis Foundation). Through its Therapy Acceleration Program, LLS has invested and partnered with many pharma/biotech to advance drugs to treat blood cancers. This could be another route to be taken or expanded to pediatric therapeutic development with drug developers. Non-profit funding for pediatric cancer research at present varies across multiple organizations. A recent ACS survey showed that among 36 organizations that responded, only 7 (including LLS) funded over $1 million annually for childhood cancer research (personal communication with ACS). Some of these organization fund research for all pediatric cancers, and therefore specific funding for pediatric leuekmias and lymphomas is far less than $1 million. Coordinated efforts would help strategically target pediatric blood cancer and advance new treatment.

3.4.1.4. Summary comments on funding

Pediatric blood cancer is rare and comprises about 0.5% of overall cancer diagnoses. However, funding for research should not be measured simply by the dollar amount proportionally to the incidents. Because cancer strikes so early in life, the years of life lost (YLL) are more profound than adult cancer patients. The average of YLL for pediatric blood cancer is about 70 years compared to adult cancer patients, which is about 10 on average. Despite dropping mortality rates, because of the significant impact on the quality of life of children and late effects, economics cannot be ignored. By that measure, our funding for pediatric cancer research is simply not acceptable. With less incentive for private pharma industry to invest in pediatric blood cancer research, it is more urgent and critical that philanthropies and the government assume the roles to develop new medicine.

3.5. Adoption of new therapeutics into effective therapies

While treatments for AML have moderate success and new therapies are highly desired, 85% of children with ALL will achieve a cure. Therefore, adoption of new therapies to treat ALL is likely to encounter resistance from patients and physicians. Ideally, an experimental therapy must include good molecular underpinnings, proven utility in animal models, a safety record that is well established (usually in adults), and ultimately, proven utility to control ALL safely based on a long-term outcome. Therefore, combination of experimental therapies into existing ALL treatment regimens are likely to be tested first and/or be tested as monotherapies in relapsed/refractory ALL patients. Moreover, we must identify high-risk populations (i.e. at risk for failure to respond to current therapies), perhaps using molecular profiling against the precise mutation, to identify candidates for experimental therapies. Models for how to include targeted therapies into front-line treatments in children can rely on examples of incorporation of dasatinib in ALL therapy, and nivolumab or brentuximab vedotin in frontline HL therapy.

4. Initiative Description

4.1. Future pediatric research

4.1.1. Strategic Short-term goals

A. Use precision medicine to match targeted therapeutic to mutation, signal transduction – hyperactivation, or unique cell surface marker in pediatric AML or ALL. Examples of this approach in pediatric blood cancers would be the use of mesothelin – ADC (grant to be activated by LLS by March 2018) (28) or CD33-, CD123-CAR T / bispecifics for AML, JAK/STAT inhibitors for hyperactivated pathways in B- ALL or T-ALL (16), CDK4/6 inhibitors in combination with corticosteroids or mTOR inhibitors (38), or RAS pathway inhibitors to control JMML (a RAS-driven tumor; pilot studies funded by LLS are underway).

B. Support small molecule development program to overcome resistance mechanisms to currently used pediatric therapies such as the use metabolic inhibitors due to hypersensitivity associated with mutations (39; LLS is currently supporting this work (A. Ferrando – Columbia University; W. Carroll - NYU).

C. Support development of recently approved therapies (e.g. daratumumab) or therapies in late stage trials in adult cancers (e.g. ulocuplumab) for use in B- or T-acute lymphoblastic leukemia. This includes generating animal model data to encourage and substantiate pediatric trials, as well as study the basis of resistance, which is likely to occur in the clinic. LLS is already funding some of this work (D. Teachey- CHOP; I. Aifantis – NYU). The work of David Teachey was recently reported (40).

D. Support the development of new CAR T therapeutics including those that 1) are directed to new cell surface targets unique to AML, ALL or other pediatric cancers 2) contain safety switches that turn-down or eliminate the action of CAR T cells when needed, 3) secrete antitumor molecules (i.e. “armored CARs”), 4) can be used off the shelf and do not require autologous T cell preparations, and 5) are cost effective.

4.1.2. Strategic Long-term goals

A. Support and perform comprehensive “Omics” analysis of 1000 patients each with clinically annotated pediatric AML and ALL to establish their “cancer omics signatures.”

B. Investigate clonal heterogeneity and disease evolution. This may have diagnostic and therapeutic implications.

C. Establish relationship between genomics and immunotherapy to help identify patient that may preferentially respond to new immunotherapies.

D. Integrate new agents, particularly immunotherapy, into front line studies (i.e. treatment-naïve patients).

E. Develop novel targeted or immuno therapies for pediatric AML, based on a more complete understanding of molecular changes unique to pediatric AML. A further

understanding of immune regulation by tumor cells is also needed and may lead to the use of novel immune modulators (e.g. checkpoint inhibitors) for therapy.

F. Develop animal tumor models that emulate human childhood diseases and predict efficacy.
G. Use a precision medicine approach in pediatric blood cancers where the mutation in the patients' tumor is matched with an existing targeted agent (both FDA-approved and those in pharmaceutical company pipelines) to block the growth of the patient's cancer.
H. Explore control of transcription factors, such as RUNX1 or MYC either by directly restoring the function of these mutated proteins, or by indirectly restoring the function of pathways controlled by these transcription factors.
I. Explore biomarkers that predict late effects as well as understand the molecular basis of post-treatment side effects. Develop (with the FDA) and implement innovative clinical trials to mitigate late effects.
J. Develop and sustain a pediatric blood cancer registry to monitor long-term treatment outcomes focused on sustained remission and assessment of side effects using new therapeutic approaches.
K. Explore the use of reduce-intensity therapy for lower risk patients; define lower-risk patients using enhanced methods.
L. Develop regulatory strategies to incentivize the rapid development of new therapies for pediatric blood cancers.

5. Timeframe

LLS' research initiative will activate new funding in FY19 and continue through FY23.

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