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Remaining challenges in childhood cancer and newer targeted therapeutics

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Summary

Despite the enormously important and gratifying advances in cancer treatment outcomes for children with cancer, cancer remains the most common cause of death from disease in children. Because the etiology and biology of cancers that occur in children differ from those that occur in adults, the immediate extrapolation of efficacy and safety of new cancer drugs to childhood cancer indications is not possible. We discuss factors that will play key roles in guiding pediatric oncologists as they select lines of research to pursue in their quest for more effective treatments for children with cancer.

Keywords

Targeted therapy; Personalized medicine; Pediatric cancer drug development; Innovative clinical trials; Preclinical testing

Introduction

The remaining challenges for childhood cancer research are best understood in the context of past advances. Treatment of childhood cancer was one of the important success stories of 20th century medicine as exemplified by the conversion of pediatric acute lymphoblastic leukemia (ALL) from an incurable disease in the 1950s to one in which over 90% of children survived five years from diagnosis, with most of these children cured of their leukemia.[1] Other cancers also have 5-year survival rates approaching or exceeding 90%, including Wilms tumor, non-Hodgkin lymphoma (NHL), Hodgkin lymphoma, and germ cell tumors. Importantly the decline in childhood cancer mortality that began in the 1960s

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continued through the first decade of the 21st century.[1] Research advances averted more than 45,000 childhood cancer deaths from 1975 to 2010.[1]

Despite the successes in identifying effective treatments for many children with cancer, approximately 2,000 children and adolescents die of their disease each year in the United States.[1] Figure 1 shows the distribution of childhood cancer mortality for children and adolescents, highlighting the contribution of leukemias, brain cancers, and neuroblastoma in younger children and the contribution of leukemias and brain cancers along with sarcomas and lymphomas in adolescents. Additionally, for some cancers progress has been very limited [e.g., diffuse intrinsic brainstem gliomas (DIPG), high-grade gliomas, and metastatic sarcomas]. Beyond the number of children who die each year, there is also the burden of long-term morbidity that diminishes quality of life for some childhood cancer survivors.

The challenge for the future is to discover and implement new strategies that will allow successful treatment of those for whom current therapeutic approaches are suboptimal, either because of insufficient efficacy or because of the damage that the treatments cause to critical normal tissues resulting in acute morbidity and long term disability. In addressing this challenge, it is important to acknowledge that most of the anticancer drug and biologic products that will be studied in the context of clinical trials in children will be ones initially developed for adult cancers. Even so, it is critical that pediatric oncologists prioritize these agents independently of their utility for adult cancers, as both the biology and the goals of treatment generally differ between childhood and adult cancers. For example, the primary goal in treating childhood cancers is cure, not palliation, whereas for many adult cancers sustained stable disease aimed at palliation is an important objective. Agents and treatment regimens that only slow tumor growth and prevent disease progression for a finite period may be valuable as adult cancer treatments, assuming that they prolong survival while allowing acceptable quality of life.[2] However, for children temporarily delaying disease progression is at best a modest success. This critical distinction between the relative benefit of cure versus palliation for children and adults with cancer, coupled with the differences in etiology and biology of pediatric and adult cancers, has implications both in terms of the cellular pathways targeted for intervention and in terms of clinical trial design. Moreover, it highlights the need for pediatric cancer prioritization decisions to focus on the biology of the cancers and on the specific needs of the children afflicted with these cancers.[2] We discuss factors below that will play key roles in guiding pediatric oncologists as they select lines of research to pursue in their quest for more effective treatments for children with cancer.

Genomic alterations as therapeutic guideposts

One essential line of research for identifying more effective treatment strategies is understanding in detail the genomic alterations that provide the blueprint for the growth and survival signaling pathways of childhood cancers. These genomic alterations highlight the genes that the cancers are most dependent upon, whether for their oncogenic driver effect or for their tumor suppressor role. Oncogenes with genomic alterations have proven among the most useful guideposts for identifying therapeutic targets as illustrated by the success of imatinib for BCR-ABL leukemias (chronic myeloid leukemia and Ph+ ALL) and the success of crizotinib for ALK-rearranged non-small cell lung cancer. The success of imatinib when

added to standard chemotherapy for children with Ph+ ALL is particularly informative. Single agent imatinib induces remissions of relatively short duration in Ph+ ALL, while standard chemotherapy is effective for a minority of children (approximately 30%). However, the combination of imatinib and standard chemotherapy was able to induce and maintain long-term remission in approximately 70% of children with Ph+ ALL.[3]

A decade ago it was possible to hope that targetable oncogenes might be identified in a high percentage of childhood cancers and that the imatinib paradigm described above could be broadly applied to other childhood cancers. At this point, thousands of childhood cancer specimens have been sequenced so that the vast majority of recurring mutations have now been identified. Targetable activated oncogenes have been identified, including the NPM-ALK fusion gene for anaplastic large cell lymphoma, ALK point mutations for a subset of neuroblastoma, BRAF genomic alterations for pediatric gliomas, Hedgehog pathway mutations for a subset of medulloblastoma, and ABL family genes activated by translocation in a subset of Ph-like ALL. However, these examples represent a small minority of all childhood cancers, making it clear that most childhood cancers do not have recurring mutations in genes that are at the present time considered targetable.

Two approaches to therapeutically targeting the “untargetable” warrant mention. One is the concept of identifying targetable susceptibilities created by untargetable genomic alterations. This concept is illustrated by the activity of EZH2 inhibitors in rhabdoid tumors. SMARCB1 loss of function through deletion or mutation is the sole recurring genomic alteration in rhabdoid tumors.[4] EZH2 is a member of the Polycomb Repressor Complex 2(PRC2) that mediates gene silencing through catalyzing trimethylation of histone 3 lysine 27 (H3K27) at the promoters of target genes.[5] Mice with conditional loss of SMARCB1 in their T-cells rapidly develop T-cell lymphomas, but tumor development is completely suppressed by concomitant loss of EZH2.[6] Small molecule inhibitors of EZH2 have been developed and have entered clinical evaluation.[7] Treatment of rhabdoid tumor xenografts with an EZH2 inhibitor led to dose-dependent tumor regression, providing evidence for the potential clinical utility of EZH2 inhibitors for cancers with SMARCB1 loss of function.[8] Another example of targetable susceptibilities created by untargetable genomic alterations is the requirement of MLL-rearranged leukemias for the DOT1L methyltransferase.[9,10] A small molecule inhibitor of DOT1L induced complete regressions in a xenograft model of MLL leukemia, and this agent has entered clinical evaluation.[11]

A second approach to targeting the untargetable is applying medicinal chemistry and high-throughput screening methods to identify small molecule inhibitors of pediatric oncogenes. This strategy is illustrated by efforts at developing small molecule inhibitors of EWS-FLI1 activity that resulted in development of YK-4-279, a small molecule that blocks EWS-FLI1 from interacting with RNA Helicase A (RHA).[12] Other pediatric oncogenes that are candidates for targeting include the PAX-FKHR fusion proteins of alveolar rhabdomyosarcoma and MYCN, which is amplified in high-risk neuroblastoma in children >18 months of age.

While genomic alterations are reliable therapeutic guideposts for many targeted agents, the role of the tissue-of-origin should not be overlooked as a potential guidepost for some

targeted agents. As an example, proteasome inhibitors are effective for patients with multiple myeloma even though mutations in proteasome subunits are exceedingly rare. The susceptibility of myeloma to proteasome inhibition likely relates to the high level of synthesis of immunoglobulins in myeloma cells, which leads to a dependence upon proteasome function to process the resulting elevated levels of unfolded proteins.[13] Similarly, inhibitors of PI3K delta are highly active in malignancies of mature B-cells not because of PIK3CD mutations, but because of the dependence of these mature B-cells upon signaling through the B-cell receptor.[14] The favorable therapeutic impact of engaging the glucocorticoid receptor in ALL cells is a pediatric example of the importance of tissue-of-origin effects.

Molecularly defined disease subtypes

A consequence of the detailed molecular characterization of childhood cancers is the recognition that single disease entities actually represent multiple clinically and biologically distinctive subtypes. For example, analysis of gene expression profiles of B-ALL cases identified 8 distinctive subtypes, one of which had similar characteristics as Ph+ ALL but lacked the BCR-ABL fusion gene,[15,16] Further investigation of this “Ph-like” ALL subset showed that these cases in turn possess a range of genomic alterations, with most having an alteration in genes involved in growth factor signaling.[17] These alterations include potentially therapeutically relevant fusion genes involving tyrosine kinases (e.g., PDGFRB, ABL1, and CSF1R), as well as well as genomic alterations involving CRLF2, JAK family members, and RAS pathway alterations.

Detailed investigation of medulloblastoma cases has identified four molecular subtypes, each with a distinctive constellation of genomic alterations as well as distinctive demographic and prognostic characteristics. One subtype, the sonic hedgehog (SHH) group, is characterized by mutations in the SHH pathway.[18] The SHH pathway can be activated by genomic alterations in a number of genes, including PTCH1, SUFU, GLI2, MYCN, and SMO. Only cases with “upstream” mutations in the SHH pathway (e.g., PTCH1 and SMO) are susceptible to inhibition by currently available SHH pathway inhibitors that block SMO action (e.g., vismodegib and sonidegib). Patients within the SHH subtype of medulloblastoma show distinctive genomic profiles by age, with infants having primarily either PTCH1 or SUFU mutations, older children having PTCH1 mutations or GLI2 amplification, and adults having primarily PTCH1 mutations.[18] For the pediatric age range, up to 50% of cases have lesions downstream of SMO that are inherently non-responsive to these agents.[18] This example highlights the complexities of targeted therapy development in children, even when a targetable oncogenic pathway is activated in a specific patient population.

Some have proposed that the molecular characterization of cancer heralds the end of the era of histology-defined treatment and the move to an era in which specific genomic alterations rather than histology will define treatment. For childhood cancers, there is reason for a more conservative approach to research strategy in which molecular characterization complements, but does not replace, histologic classification of cancers. One reason for this conservative approach is the remarkable relationship between specific genomic alterations

and specific cancer types, as illustrated by the finding of H3F3A K27M mutations in midline high grade gliomas of children but in virtually no other cancers.[19] Similarly, BRAF mutations do not occur randomly across childhood cancers, but are found primarily among cases of low-grade gliomas.[20] A second reason for skepticism is that the therapeutic implications of genomic alterations can be cell context dependent, as illustrated by the high activity of BRAF inhibitors for melanoma patients with BRAF V600E mutations, but their low activity in colorectal patients with the same mutation.[21] A final note of caution that is particularly relevant for childhood cancers is that the development pathway for targeted agents that show single agent activity will likely be (at least initially) through their integration with standard therapy, as illustrated by the imatinib example for Ph+ ALL described above. To the extent that different histologies have different standard treatments, the development of targeted agents will be accordingly segregated by histology.

Immunotherapy strategies

Immunotherapeutic approaches to cancer treatment are revolutionizing treatment for some adult cancers. Examples include monoclonal antibodies targeting overexpressed cancer cell proteins (e.g., the HER2-targeted agent herceptin for HER2-amplified breast cancer), antibody-drug conjugates (e.g., the CD30- targeted agent brentuximab vedotin for Hodgkin lymphoma and trastuzumab emtansine for HER2-amplified breast cancer), and checkpoint inhibitors (e.g., the CTLA-4 targeted agent ipilimumab for advanced melanoma and anti-PD1 targeted agents for non-small cell lung cancer and melanoma). Evaluating immunotherapeutic approaches is an important line of pediatric oncology research. ch14.18 (a monoclonal antibody targeting GD2 on neuroblastoma cells) was identified in a phase 3 trial as effective for children with high risk neuroblastoma.[22] Brentuximab vedotin is highly active as a single agent against relapsed/refractory CD30-expressing malignancies such as Hodgkin lymphoma and anaplastic large cell lymphoma, and clinical trials in children evaluating its contribution when added to standard chemotherapy for each of these conditions are underway. A number of other pediatric-relevant antibody-drug conjugates have entered clinical trials for adult cancers, including agents targeting CD19, CD22, CD33, and CD56. It is anticipated that these agents will be evaluated in children with cancers expressing these antigens. Checkpoint inhibitors entered pediatric evaluation through a phase 1 evaluation of ipilimumab, and clinical trials to evaluate efficacy in specific pediatric cancers are planned. Early phase clinical trials for other checkpoint inhibitors in children are underway or being planned. Given the remarkable activity observed for checkpoint inhibitors for several disparate adult cancers, it will be important to determine whether there are comparable pediatric populations that can benefit from checkpoint inhibition. Given the non-overlapping toxicity profiles of this class of drugs when compared to conventional cytotoxic agents, the potential for combinatorial approaches to therapy is significant.

Other immunotherapy strategies that have entered pediatric evaluation include bispecific T-cell engager (BiTE) antibodies and chimeric antigen receptor (CAR) T-cells. Proof of principle for each of these strategies has been achieved through clinical trials for CD19-expressing B-ALL in adults and children. Blinatumomab is a BiTE antibody with two binding sites: one for CD3 on T-cells and the other for CD19 on the surface of B-ALL cells. The close juxtaposition of the T-cell and leukemia cell is sufficient to trigged T-cell

mediated cytotoxicity. Blinatumomab induces remission in a substantial proportion of adults and children with multiply relapsed B-ALL.[23] A phase 3 clinical trial is evaluating its incorporation into salvage therapy for children with ALL in first relapse. CARs are engineered receptors that can target surface molecules and that can engage molecular structures independent of MHC. CAR T-cells targeting CD19 have shown high complete remission rates in children and adults with relapsed/refractory B-ALL.[24]

Prioritizing agents for clinical evaluation

Childhood cancer clinical research is limited by the thankfully relatively small numbers of children with any individual type of cancer. As a result, only a small subset of the hundreds of anticancer agents under development for adult cancers will ever be studied in children. For individual cancers no more than two agents can undergo definitive testing through phase 3 evaluations in a decade. Hence, successful prioritization decisions that move truly effective agents to definitive testing are critical to curing more children, as moving ineffective agents forward for definitive testing blocks progress during the period in which they are tested.

One aspect of prioritization is identifying the target/pathway that is of highest priority for clinical evaluation for a specific childhood cancer. As noted earlier, recurring genomic alterations identify targets/pathways that cancer cells are dependent upon and have been good guideposts for successful prioritization. A second aspect of prioritization of targets/pathways is the preclinical testing of agents against childhood cancer models, although multiple caveats apply. While in vitro testing can be informative, it provides limited evidence for therapeutic window. The potential for over-prediction for clinical activity is high when claims are made for sensitivity to the test agent based on sustained in vitro exposure to concentrations of the agent that are not achievable in humans (or if achievable, are maintained for only brief periods).

In vivo testing, using either xenografts or genetically engineered models, can make important contributions to the prioritization process, although cautionary notes apply here as well. The preclinical models employed for testing need to replicate the key molecular characteristics of the cancers that they are meant to represent. The detailed molecular profiling of preclinical models is essential in the era of molecularly targeted therapies, as particular agents are likely to have activity only against models with corresponding specific genomic alterations. The testing results for a MEK inhibitor evaluated against a large panel of pediatric xenografts illustrates this point, as the only responding xenograft was one with a BRAF V600E mutation.[25] A second caveat for in vivo testing using xenografts is that the drug exposures observed in mice at the dose/schedule of the agent employed preclinically need to match those achievable in humans. A common cause for over-prediction of clinical activity by in vivo testing results is the tolerance of mice to higher drug exposures for the tested agent compared to those tolerated in humans. It is possible to minimize false positive predictions of clinical activity resulting from greater tolerance of mice for anticancer agents by reducing the dose of the tested agents so that the drug levels in mice more closely approximate those achievable in humans.[26,27] Pharmacokinetic-pharmacodynamic (PK-PD) models can also be developed that characterize the relationship between drug concentration

and antitumor activity in dose-ranging xenograft experiments, with the PK-PD models then employed to assess whether drug exposure profiles observed in humans match those associated with activity in rodents.[28,29] A final cautionary note regarding the predictive value of *in vivo* preclinical models to predict for clinical activity relates to the use of clinically relevant criteria for claiming antitumor activity. Publications describing preclinical testing results often include claims of agent activity based on tumor growth delay (sometimes very modest delay), which in the clinical setting would be defined as progressive disease. For childhood cancer in vivo preclinical testing, tumor regressions are felt to be the best predictor of likely clinically relevant activity. As noted earlier, the goal of treatment for childhood cancers is cure, and the pathway to cure must go through complete response, whether achieved by chemotherapy, radiotherapy, or surgery. Pediatric relevant examples of agents that induce objective responses both in preclinical models and in the clinic include topoisomerase I inhibitors for neuroblastoma,[27] crizotinib for ALK-rearranged tumors,[30,31] dasatinib for BCR-ABL ALL,[32] sorafenib for FLT3-ITD leukemias, [33–35] and MEK inhibitors for BRAF mutated cancers.[25,36]

It is critical for prioritization to not only occur between agents targeting different pathways but also between agents within the same therapeutic class. For example, at one time more than a dozen IGF-1R targeted agents were in clinical development, and Ewing sarcoma was an obvious disease of interest for these agents. Conducting single agent phase 1 and even phase 2 trials for Ewing sarcoma was possible for several of these agents as only 20–30 patients were needed per agent for these clinical trials. However, conducting a definitive study to show that one of these agents improved outcome when added to standard therapy for patients with Ewing sarcoma would have require hundreds of patients, such that no more than one agent could have been feasibly studied in North America. The IGF-1R pathway is not unique in having multiple agents targeting it enter clinical development, as the same issue applies to checkpoint inhibitors, MEK inhibitors, ALK inhibitors, BRAF inhibitors, SMO inhibitors, immunoconjugates and other classes of agents including CAR-T cells. The issue of prioritization within class will have to be addressed for each of these classes of agents as they move further into pediatric testing.

Clinical trials in the era of precision medicine

Pediatric oncologists have been at the forefront of applying the “precision medicine” concept in the clinic. As noted in a National Academy of Sciences report, precision medicine “does not literally mean the creation of drugs or medical devices that are unique to a patient, but rather the ability to classify individuals into subpopulations that differ in their susceptibility to a particular disease, in the biology and/or prognosis of those diseases they may develop, or in their response to a specific treatment”. Childhood cancer clinical trials have for years utilized molecular characteristics of cancers to assign patients to particular clinical trials and to particular treatments (e.g., MYCN for neuroblastoma, and hyperdiploidy and ETV6-RUNX1 for ALL, and FLT3-ITD for AML). A consequence of applying precision medicine concepts to childhood cancers is that the patient populations appropriate for evaluation get smaller and smaller, which has important consequences for clinical trial design.

The development of imatinib for Ph^+ ALL in children illustrates one approach to addressing the challenge of smaller and smaller patient populations.[37] In this case, results from a single arm study demonstrated that imatinib added benefit to standard therapy. The extent to which this example can be replicated for other agent/biomarker combinations will depend in part on the extent to which the following factors are similarly represented:

- Imatinib had substantial single agent activity for the target patient population, increasing confidence that any effects observed with its addition to standard therapy were likely to be true effects.
- There was a reasonably large, recent historical control population that allowed a comparison to be made between outcome for standard therapy with and without the addition of imatinib.
- The treatment effect observed with the addition of imatinib was large (3-year EFS of 80% ± 11% versus 35% ± 4% for the addition of imatinib compared to historical controls, respectively).[37]

An example of applying the historical control approach to identify the contribution of novel agents added to standard therapy is ANHL12P1 (NCT01979536), a randomized phase 2 clinical trial for children with anaplastic large cell lymphoma. This population is characterized by their genomic lesion (an ALK fusion gene) and by their uniform expression of the surface protein CD30, making these patients responsive to both crizotinib and brentuximab vedotin.[38,39] Patients enrolled on ANHL12P1 receive standard therapy plus either crizotinib or brentuximab vedotin, and a total of approximately 140 patients are to be enrolled. The primary outcome measure is a comparison of the EFS for each arm to the estimated EFS for chemotherapy alone, such that with 70 or fewer patients per arm, one or both arms may be identified as superior to chemotherapy alone.

Often sufficiently large historical controls will not be available for molecularly defined patient populations, and so alternative trial designs will need to be considered when targeted agents are evaluated for these patient populations. One alternative design for small patient populations is randomization, with reductions in the number of patients required achieved by either targeting large treatment effects, or by using inflated Type I error rates, or both. When large treatment effects are targeted, the number of patients required can be markedly reduced as illustrated by a clinical trial of a scorpion anti-venom in children using a randomized design with a minimum sample size of 14 patients.[40] Likewise, inflating type I error rates beyond the standard two-sided 0.05 reduces the numbers of patients required for any given targeted effect size.[41]

A requirement for pediatric precision medicine is a childhood cancer clinical trials infrastructure proficient in evaluating new therapies in genomically defined subtypes of childhood cancers. Pediatric oncologists have a history of rapidly adopting new technologies that provide prognostic and/or therapeutic insights for their patients, and so adoption of next generation sequencing methods to clinical specimens to molecularly define relevant patient populations will likely occur quickly. The greater challenge will be addressing the relatively limited numbers of children with genomically defined subtypes of a given cancer diagnosis. More than ever cohesion within the pediatric oncology community will be needed, since

clinical trials for small populations that would be challenging with widespread participation will become impossible if the population is fragmented by multiple research teams all trying to study the same small group of patients. International collaborations will be increasingly needed so that sufficient patients with specific genomic characteristics can be enrolled onto clinical trials to define the contribution of novel agents for these patient populations.

Incentivizing development of pediatric-specific agents

A corollary of the observation that distinctive genomic alterations not found in adult cancers drive some childhood cancers is that mechanisms need to be developed to identify and develop agents that selectively block the oncogenic activity of these unique childhood cancer therapeutic targets. Development of ch14.18 for neuroblastoma may provide a blueprint for how such agents can be developed.[22] In this case, public funds were used to discover the therapeutic target and develop the agent through phase 1, 2, and 3 clinical trials. The successful phase 3 trial sufficiently "de-risked" ch14.18 to the extent that a biotechnology company could commit to supporting the multiple additional steps required for submitting a Biologics License Application (BLA). As well, recent legislative initiatives such as the "Creating Hope Act" may stimulate development of childhood cancer specific agents by providing an incentive to industry by issuing transferrable priority review vouchers when drugs are developed and approved for specific pediatric rare diseases including cancers.[42] The first priority review voucher was recently sold for $67.5 million, supporting the utility of the program as a means for incentivizing pharmaceutical companies to develop "pediatric specific" agents.

More generally regarding the role of FDA, provisions of the 2012 Food and Drug Administration Safety and Innovation Act (FDASIA), including the permanent reauthorization of the Best Pharmaceuticals for Children Act (BPCA) and the Pediatric Research Equity Act (PREA), have the potential to accelerate the evaluation of new therapies for childhood cancers since there is now a requirement to consider and discuss pediatric development plans at "end of phase 2 meetings" for new agents under development for adult malignancies. This should lead to the generation and issuance of Written Requests for pediatric evaluations at an earlier point in the drug development timeline.

Conclusions

The genomic discoveries of the past decade have provided biological insights that were hardly imaginable even two decades ago. Translating these insights into more effective treatments is well-advanced for some patient populations, but barely initiated for others. A multitude of challenges will need to be addressed, ranging from prioritizing from among agents under development for adult cancers to developing agents specific for pediatric cancer targets. More than ever a unified effort is needed for the definitive testing of agents for their ability to cure more children with cancer. Future progress will require the ingenuity, insight and dedication of a new generation of pediatric oncologists to build upon past discoveries and to make critical new discovers so that the goal of curative therapy for every child with cancer is achieved.

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Key Points

1. There are only a limited number of druggable molecular targets identified to date in childhood cancers. Nonetheless, evaluation of inhibitors of those which have been identified is warranted in relevant tumor types and subsets of patients
2. The principle of integration of active targeted therapy with best available therapy has been established and will likely be the basis for future investigations and hopefully advances.
3. Strong biologic rationale and preclinical data, particularly from in vivo testing, are central to effective prioritization of agents for clinical evaluation.
4. Prioritization of “same in class” products will be a persistent challenge but is essential for effective pediatric cancer drug development strategies.
5. Increased, effective communication and collaboration between clinical investigators, industry and international regulatory agencies are essential for the development of successful clinical research plans and improved drug development opportunities.

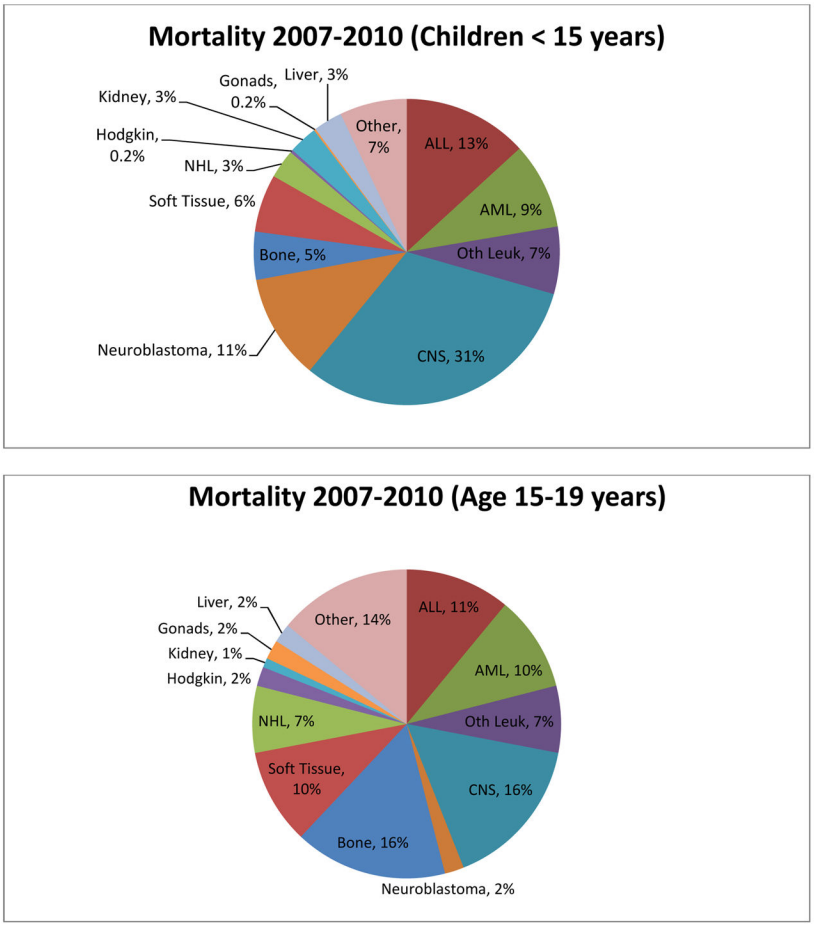

Figure 1.

Patterns of mortality for children and adolescents < 15 years and 15–19 years for 2007–2010. ALL = acute lymphoblastic leukemia, AML = acute myeloid leukemia, Oth Leuk = other leukemia, NHL = non-Hodgkin lymphoma. Adapted from Smith MA, Altekruse SF, Adamson PC, Reaman GH, Seibel NL. Declining childhood and adolescent cancer mortality. *Cancer*. 2014;120(16):2497–2506; with permission.