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REVIEW

Lessons From the Past: Opportunities to Improve Childhood Cancer Survivor Care Through Outcomes Investigations of Historical Therapeutic Approaches for Pediatric Hematological Malignancies

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Investigations of long-term outcomes have been instrumental in designing safer and more effective contemporary therapies for pediatric hematological malignancies. Despite the significant therapeutic changes that have occurred over the last five decades, therapy modifications largely represent refinements of treatment protocols using agents and modalities that have been available for more than 30 years. This review summarizes major trends in the evolution of treatment of pediatric hematological malignancies since 1960 to support the relevance of the study of late effects of historical therapeutic approaches to the design and evaluation of contemporary treatment protocols and the follow-up of present-day survivors.
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Key words: childhood cancer therapy; late effects; long-term follow-up

INTRODUCTION

Progress in therapy for pediatric hematological malignancies over the last five decades has resulted in remarkable gains in survival for children afflicted by these diseases. Five year survival exceeds 85% for children with acute lymphoblastic leukemia (ALL), non-Hodgkin lymphoma (NHL), and Hodgkin lymphoma (HL) and has reached 60% for those with acute myeloid leukemia (AML) [1]. This success resulted from discoveries that stimulated changes in therapeutic approaches over the last five decades. Increased understanding of cancer biology led to the improved diagnosis, risk assessment, disease monitoring, and treatment, as well as the discovery of therapeutic targets for drug development. More precise, non-invasive imaging technology facilitated non-surgical staging for children with HL. Appreciation of both acute and late modality-specific toxicities motivated investigations to elucidate the pathophysiology and risk factors for treatment-related morbidity and mortality. The results of these studies have played a critical role in the evolution of pediatric cancer treatment approaches and informed risk counseling and health screening recommendations of long-term survivors.

Contemporary therapy for the majority of pediatric malignancies is risk-adapted, based on a variety of clinical, biological, and genetic factors, and more recently, also on early treatment response. While novel biological and molecularly targeted agents are the subjects of ongoing research, cytotoxic chemotherapy, and irradiation continue to be used for the treatment of the majority of children diagnosed with cancer. Evaluation of late health outcomes of survivors treated with these modifications is important to characterize their subsequent health. However, one may debate how relevant the study of late effects of historical therapeutic approaches is to the design and evaluation of contemporary treatment protocols and follow-up of present-day survivors. Using data from representative pediatric cancer trials, this review will address this issue by: (1) summarizing major trends in the evolution of treatment of pediatric hematological malignancies since 1960; (2) identifying treatment-specific exposures in historic cohorts from the four decades before 2000 that have relevance to clinical trials in the past decade; and (3) determining the extent to which the study of retrospective cohorts of long-term survivors can be used to inform the anticipated risks of late effects in patients under active treatment.

ACUTE LYMPHOBLASTIC LEUKEMIA

ALL was one of the first cancers to respond to chemotherapy and the first disseminated cancer that became curable (Table I). In the late 1940s, aminopterin was shown to induce temporary remissions of ALL [2]. The identification of additional chemotherapeutic agents, together with improved supportive care during the 1950s and 1960s, facilitated the development of combination chemotherapy regimens, which ultimately made childhood ALL a highly curable disease [3]. Notably, vincristine, prednisone, mercaptopurine, methotrexate, and cyclophosphamide, drugs used in the seminal St. Jude study [4], continue to form the backbone of contemporary therapy.

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TABLE I. Evolution of Therapy for Acute Lymphoblastic Leukemia

Treatment modality	Decade					Historic treatment modalities used in contemporary therapy
	1960	1970	1980	1990	Post-2000	
Chemotherapy Agents	• Antimetabolites (methotrexate, mercaptopurine), asparaginase, corticosteroids, and vinca alkaloids used in combination • Early use of cyclophosphamide	• Widespread use of induction/consolidation/ maintenance strategy • Increased use of anthracyclines for high risk patients	• Asparaginase intensification within DFCI consortium • Epipodophyllotoxins abandoned for most children with ALL • No widely used new agents	• Introduction of imatinib for small subset of patients with Philadelphia positive ALL • Nelarabine introduced for T-cell ALL • Dexamethasone more widely used in induction therapy	• Additional refinement of risk based therapy • No new agents added to initial therapeutic modalities	• Prednisone • Vincristine • Daunomycin/doxorubicin • Cyclophosphamide • L-Asparaginase • Methotrexate • Mercaptopurine
Dose-intensity/ duration	• Modest dose intensity • Long maintenance therapy (3–5 years)	• Intensity of drugs increased based on early BFM trials showing benefit of delayed intensification for all subsets of ALL patients	• Further intensification for high risk children • Use of "double DI" • Duration of therapy constant	• Focus on stratification and application of intensified regimens to more limited subsets	• Intensity of therapy remains constant • Duration continues to be constant	• Induction • Consolidation • Delayed intensification • Maintenance – 2 years for girls – 2.5 years for boys
Radiation Therapy	• Early use of cranial and craniospinal irradiation	• Trials of extended field irradiation • Reduced use of spinal irradiation	• Randomized trials show efficacy of CNS chemoprophylaxis • Reduced use of radiation therapy for SR children who are CNS negative	• Further reduction in use of preventive irradiation • High risk patients no longer routinely irradiated Dose remains constant at 18 Gy for prophylaxis; reduced doses investigated for T-cell ALL and CNS relapse	• Further reduction in indications for radiation therapy	• Cranial irradiation limited to CNS disease refractory to systemic and intrathecal chemotherapy

ALL, acute lymphoblastic leukemia; BFM, Berlin–Frankfurt–Münster; CNS, central nervous system; DFCI, Dana–Farber Cancer Institute; DI, delayed intensification.

The initial clinical trials in the 1960s demonstrated that remissions could be sustained after cessation of therapy in only a small number of children [4]. In the late 1960s and early 1970s, Pinkel and coworkers recognized ''central nervous system (CNS) relapse'' as the major obstacle for cure. The introduction of presymptomatic (''prophylactic'') CNS irradiation [5], in combination with prolonged ''maintenance'' antimetabolite therapy (methotrexate and mercaptopurine) resulted in long-lasting remission in approximately 50% of children [5,6]. The addition of other agents including anthracyclines (daunorubicin) and L-asparaginase to those regimens during the 1970s completed the portfolio of drugs that most children with ALL receive today [7].

Two major treatment advances were made in the 1980s. The Berlin–Frankfurt–Münster (BFM) group introduced a re-intensification phase of chemotherapy that basically repeated the initial remission induction and improved the cure rate to approximately 70% [8]. With its efficacy confirmed by multiple clinical trials worldwide, this treatment phase (variously named as delayed intensification or reinduction) has now become an integral component of contemporary protocols [9]. The other advance was the demonstration that intensified intrathecal chemotherapy could sustain CNS remissions *without* the use of cranial irradiation in patients with ''standard-risk'' ALL [10–12]. During this time, the topoisomerase II inhibitors, etoposide and teniposide, were added to ALL therapy, but their use is now restricted to patients with refractory or relapsed leukemia because of their leukemogenic effect [13].

More recent advances in ALL therapy have come from refined use of these agents. Corticosteroids remain a mainstay of therapy, but dexamethasone has replaced prednisone in many clinical trials because it is associated with a lower risk of systemic and CNS relapse [14,15]. Intensification of L-asparaginase therapy has also become more widely used, especially in patients with T-cell or high-risk ALL [15], and has been facilitated by the approval of pegylated-asparaginase, a long-acting form of the drug [16]. Philadelphia chromosome-positive ALL has become the first genetic subtype that is benefitted from targeted therapy with imatinib, a selective inhibitor of the BCR-ABL1 tyrosine kinase [17]. The use of the purine nucleoside analog nelarabine is under investigation for children with T-cell disease [18].

The fundamental components of curative treatment have changed very little since the 1980s. Children are still treated with essentially the same chemotherapy drugs in phases of induction, consolidation, delayed intensification, and maintenance. However, risk stratification is more precise with the use of minimal residual disease assessment after remission induction to avoid over- or under-treatment [19]. Induction has changed only with the more widespread use of dexamethasone and pegylated-asparaginase. Consolidation phase includes intrathecal therapy and high-dose methotrexate plus mercaptopurine. Prolonged delayed intensification is not needed for standard- or intermediate-risk patients with good early treatment response to remission induction [20]. Maintenance therapy continues to be antimetabolite based. Clearly, the use and the dose of presymptomatic radiotherapy can be reduced, and, in fact, could be totally replaced by effective systemic and intrathecal chemotherapy [19]. Recent findings that link pharmacogenomic variations with drug exposure, efficacy and toxicity should lead to ''personalized therapy'' for individual patients in the future.

ACUTE MYELOID LEUKEMIA

In the 1960s, chemotherapy regimens for acute AML were similar to those for ALL and produced brief complete remissions at rates well below 50% and long-term survival in less than 5% [21] (Table II). During the early treatment years, it was recognized that about 15% of patients with AML presented with CNS disease, but CNS prophylaxis was not routinely administered [22,23].

In the 1970s, treatment protocols that incorporated anthracyclines in lieu of alkylating agents resulted in remission rates that exceeded 50%, but with minimal advances in long-term survival [23]. Subsequent trials using more aggressive antimetabolite therapy produced 5-year survival rates exceeding 15% [22]. By the end of the 1970s, the two-drug combination of cytarabine and daunorubicin, known as ''7 and 3,'' became the standard, resulting in remission in 75–80% of patients and 5-year survival for almost 30% when followed by maintenance [24]. Cranial irradiation was utilized for treatment and prevention of CNS leukemia [24]. A study in the late 1970s showing allogeneic hematopoietic cell transplantation (HCT) with matched-related donors (MRDs) yielded better outcome in children and young adults [25], prompting a series of ''biologically randomized'' trials that allocated all individuals with MRDs to a transplant arm, with others assigned or randomized to one or more chemotherapy-based regimens including autologous HCT [24,26–28]; these studies generally demonstrated that allogeneic HCT was superior.

In the 1980s, chemotherapy for patients with AML was further intensified. Etoposide was introduced into induction and post-remission therapy [27,29]. The dose of cytarabine was escalated substantially (HD-AraC) and proved to be safe [30]. HD-Ara-C commonly led to prolonged myelosuppression and gastrointestinal toxicity, and less frequently to acute CNS and/or lung toxicity, but long-term side effects other than CNS sequelae have not been established. North American studies showed that remission induction with intensively-timed HD-Ara-C obviated the need for prolonged post-remission therapy [27,31]. With the use of HCT, overall 5-year survival rates increased to 35% in the 1980s [24,27]. Prophylactic cranial irradiation was also abandoned during this decade based on studies demonstrating comparable outcomes with the use of intrathecal cytarabine [27,32].

In the 1990s, research focused on the impact of 3 to 5 total courses of intensified induction on long-term survival. North American protocols utilized intensively timed induction cycles [26,28,33]. European protocols increased chemotherapy doses [34] or the number of days of drug administration from 7 to 10 [35]. Both approaches improved long-term survival rates to 50% or higher [28,34,35]. Escalating chemotherapy intensity and paying strict attention to supportive care for infections further improved survival in excess of 60% [26,36,37]. Although European and North American investigations reported comparable long-term survival rates, North American cooperative group trials generally prescribed daunorubicin dose-equivalents of 350 mg/m^2 or less [24,26,27,33], whereas Europeans investigators utilized total anthracycline doses that exceeded 400 mg/m^2 [34–37]. Demonstration of greater risk of long-term cardiotoxicity after cumulative anthracycline doses of 300 mg/m^2 and higher should drive lower dosing in future trials [38–40].

Recognition of excess transplant-related morbidity and mortality, often associated with acute and/or chronic graft-versus-host

TABLE II. Evolution of Therapy for Acute Myeloid Leukemia

Treatment modality	Decade					Historic treatment modalities used in contemporary therapy
	1960	1970	1980	1990	Post-2000	
Chemotherapy Agents	• Vincristine • 6 Mercaptopurine • Corticosteroids • Cyclophosphamide • Ara-C	• Ara-C • Anthracyclines • 6 Thioguanine • Other anti-metabolites	• High dose Ara-C • Etoposide	• ATRA for APL	• Increasing stratification of therapy based on traditional risk factors or molecular markers	• High dose Ara-C • Daunomycin • Etoposide
Dose-intensity/ duration	• Low doses over 3–5 years	• Low doses over 1.5–4 years	• 6-8 months with aggressive post-remission therapy • Randomized trials show maintenance chemo reduces overall survival	• 3–4 aggressive courses total over 4–6 months		• 3–4 aggressive courses total over 4–6 months
CNS prophylaxis/ treatment	• None/IT Ara-C • Lumbar punctures for symptomatic patients only	• Prophylactic cranial irradiation	• IT Ara-C/IT Ara-C-methotrexate-hydrocortisone (“Triples”)		• Considering ↑ IT chemotherapy for patients at high risk	• Intrathecal Ara-C
Bone marrow transplantation	• Not available	• Experimental, with matched family donors only	• Several “biologic randomized” trials showing superiority of allogeneic HCT over chemotherapy	• Busulfan/ cyclophosphamide for HCT conditioning	• Use of alternative transplants for high risk patients in first CR	• HCT reserved for high risk (unfavorable cytogenetics or residual/refractory disease after induction)
Radiation Therapy	• Treatment of granulocytic sarcoma (chloroma) only	• Prophylactic cranial irradiation	• Radiation therapy used only for CNS relapse and granulocytic sarcoma	• No CNS irradiation, even at initial relapse • Radiation therapy only for granulocytic sarcoma compromising organ function		• Irradiation limited to CNS disease refractory to systemic chemotherapy or granulocytic sarcoma compromising organ function

APL, acute promyelocytic leukemia; Ara-C, cytosine arabinoside; ATRA, all trans-retinoic acid; CNS, central nervous system; CR, complete remission; HCT, hematopoietic cell transplantation; IT, intrathecal.

disease (GVHD) [41], motivated evaluation of prognostic markers, especially cytogenetics, to identify patients who did not require HCT to optimize survival [42]. These studies demonstrated that individuals with favorable cytogenetics, for example, inv(16q) or t(8;21), had comparable outcomes after treatment with chemotherapy or HCT [42], whereas HCT improved outcome of individuals with intermediate-risk AML [43]. Because patients with high-risk AML (e.g., unfavorable cytogenetics such as monosomy 5 or 7, or residual disease after induction) did very poorly after treatment with standard chemotherapy [42], HCT became the standard of care for all such individuals once a remission was achieved. If an MRD was not available, alternate donor sources including matched unrelated [44], unrelated cord blood [45], or haplo-identical donors [46] were utilized.

Elucidation of the molecular biology of specific subtypes of acute leukemia led to the development of targeted therapeutic approaches for selected subsets of AML [47,48]. As better molecular characterization of AML identifies specific molecular targets such as FLT3 [49], long-term survival for other AML subtypes may exceed the 60–65% rates established by the end of the 1990s [26,36,37]. Guided by minimal residual disease detection, the indications, and the types of donor utilized for HCT have evolved [50]. Radiation therapy is used rarely, including that in pre-transplant conditioning regimens. Lessons from the past four decades have led to the standard administration of cytarabine and topoisomerase II inhibitors (anthracyclines, etoposide), which, when applied intensively, cure over 60% of children with AML.

HODGKIN LYMPHOMA

Radiation therapy, when delivered at established tumoricidal doses (35–44 Gy) to consistent treatment fields of contiguous lymph nodes, was the first modality to produce prolonged disease-free survival in patients with HL [51] (Table III). During the 1960s and early 1970s, pediatric and adult patients were treated in a similar fashion with high-dose radiation delivered to treatment volumes routinely extended to encompass adjacent uninvolved nodal regions. This approach cured a significant number of patients with localized disease, but was suboptimal for those with advanced-stage and/or bulky nodal disease.

The development of the combination of mechlorethamine, vincristine (Oncovin), procarbazine, and prednisone (MOPP) in the 1960s [52], and recognition of the adverse effects of high-dose radiation therapy on musculoskeletal development in pediatric survivors motivated the first investigations of combined-modality therapy in children with HL [53]. Pediatric trials in the 1970s evaluated whether multiple cycles of chemotherapy could replace a portion of the radiation therapy in laparotomy-staged children. The ensuing combined modality trials prescribed multi-agent chemotherapy and lower radiation doses (15–25.5 Gy) to reduced treatment volumes [54]. The development of the ABVD [doxorubicin (Adriamycin), bleomycin, vinblastine, dacarbazine] regimen [55] and the desire to avoid MOPP-related sequelae of infertility and secondary leukemia led to MOPP-derivative regimens (e.g., COPP) that substituted less leukemogenic and gonadotoxic alkylating agents (e.g., cyclophosphamide) for mechlorethamine or alternated ABVD to reduce cumulative alkylating agent dose exposure [56–58]. The antineoplastic activity of ABVD proved to be superior to MOPP [59], but was associated with cardiopulmonary toxicity related to doxorubicin and bleomycin [60].

By the end of the 1980s, the use of standard-dose radiation therapy alone was generally recommended only for older patients with localized disease who had achieved skeletal maturity. Surgical staging was favored for these patients to assure appropriate treatment planning, whereas clinical staging became standard of care for younger children and those with advanced-stage disease whose treatment planning routinely included systemic therapy. Demonstration of the effectiveness of combined-modality therapy, concurrent with advances in diagnostic imaging technology, led to the acceptance of clinical staging for all patients, thus avoiding the life-long health risks associated with splenectomy.

In the 1990s, treatment modifications were undertaken to prevent cardiac toxicity in very young children, preserve gonadal function in boys, and reduce breast cancer risk in girls. Pediatric HL regimens uniformly prescribed combination chemotherapy with or without low-dose involved field radiation and the use of radiation therapy as a single modality was abandoned. The cumulative dose of anthracycline was limited to $\leq$300 mg/m^2, the threshold dose linked with the highest risk for cardiotoxicity in pediatric cohorts [61]. Etoposide was incorporated into treatment regimens as an effective alternative to alkylating agents to reduce gonadal toxicity and enhance antineoplastic activity [62–64]. Abbreviated and dose-dense regimens were introduced to determine if rapid induction of tumor response would permit reduction of cumulative chemotherapy doses or elimination of radiation therapy altogether [62,63]. Ultimately, a risk-adapted, response-based treatment approach evolved that titrated the length and intensity of chemotherapy and dose of radiation based on disease-related factors including stage, number of involved nodal regions, tumor bulk, the presence of B symptoms, and early response to chemotherapy by functional imaging.

Evaluation of the late health outcomes of survivors treated during the last five decades still has relevance to treatment planning for newly diagnosed children and counseling of long-term survivors. Low-dose, involved field irradiation, initially integrated into combined modality trials 40 years ago, remains an important modality in optimizing disease control for many patients. Likewise, all of the agents in original MOPP and ABVD regimens continue to be used in treatment regimens today. Although cyclophosphamide has almost uniformly replaced mechlorethamine as the preferred alkylator regimen in most trials, nitrogen mustard is still used in limited doses in novel regimens developed in the 1990s [65]. Administration of restricted chemotherapy cycles of these combinations remains an integral component of risk-adapted therapy for newly diagnosed children.

NON-HODGKIN LYMPHOMA

Over the past 50 years, improvement in treatment outcomes for children with NHL has largely been accomplished through the development and refinement of risk-adapted, histology- or immunophenotype-directed therapy [66–69] (Table IV). Diverse treatment approaches were utilized in the 1960s and 1970s, which in some cases included regimens used for the treatment of ALL [70–74]. These trials featured multi-agent regimens like the 10-drug combination, LSA2L2 [74], and the cyclophosphamide, vincristine, methotrexate, prednisone (COMP) regimen [71].

TABLE III. Evolution of Therapy for Pediatric Hodgkin Lymphoma

Treatment modality	Decade					Historic treatment modalities used in contemporary therapy
	1960	1970	1980	1990	Post-2000	
Chemotherapy/ agents	• Introduction of MOPP—first non-cross-resistant chemotherapy combination	• Introduction of alternative non-cross resistant ABVD combination • Introduction of MOPP derivative COPP, substituting cyclophosphamide for more toxic mechlorethamine	• Use of regimens alternating MOPP and ABVD (or derivatives) to reduce exposure to agents with dose-related toxicity	• Introduction of risk-adapted regimens • Use of etoposide as alternative to alkylating agents to reduce gonadal toxicity and enhance antitumor activity	• Use of risk-adapted and response-based regimens • Combination chemotherapy without alkylators for localized/ favorable disease • Combination chemotherapy with alkylators for advanced/ unfavorable disease • Introduction of alternate non-cross-resistant regimens for slow responders	• Nitrogen mustard • Vincristine (Oncovin) • Prednisone • Procarbazine • Doxorubicin • Bleomycin • Vinblastine • Dacarbazine • Etoposide
Dose-intensity/ duration	• Standard treatment with two cycles beyond remission	• 6–12 cycles	• 4–6 cycles based on presenting features	• Introduction of abbreviated dose-dense chemotherapy – 2–4 cycles for favorable/localized – 4–6 cycles for unfavorable/advanced • Duration (# cycles) based on early response		• Risk-based, response-based • Dose-dense regimens
Radiation therapy	• Definition of tumoricidal dose (35–40 Gy) and standard treatment fields of contiguous lymph nodes • Extended treatment fields	• Extended treatment fields • Radiation therapy (35–40 Gy) as single modality favored for skeletally mature children with localized disease • Low-dose (15–25.5 Gy) irradiation used with combination chemotherapy		• Abandonment of high-dose radiation therapy alone • Low-dose (15–25.5 Gy) involved-field applied in conjunction with chemotherapy	• Low-dose (15–25.5 Gy) involved-field targeting to involved (targeted) nodes • Response-based • No irradiation if early complete response in selected cases	• Low-dose (15–25.5 Gy) involved-field to Involved (targeted) nodes
Staging	• Laparotomy staging with splenectomy		• Laparotomy staging with splenectomy limited to those with localized clinical staging	• Clinical staging with computed tomography and functional imaging (gallium)	• Clinical staging with computed tomography and functional imaging (positron emission tomography)	• Routine clinical staging with anatomic (CT) and functional imaging (PET) Surgical biopsy of equivocal staging findings only if results significantly impact treatment assignment

ABVD, doxorubicin (Adriamycin), bleomycin, vinblastine, dacarbazine; MOPP, mechlorethamine, vincristine (Oncovin), procarbazine, prednisone.

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TABLE IV. Evolution of Therapy for Non-Hodgkin Lymphoma

Treatment modality	Decade					Historic treatment modalities used in contemporary therapy
	1960	1970	1980	1990	Post-2000	
Chemotherapy/ agents	• Non-protocol or as per ALL regimens • Antimetabolites (methotrexate, mercaptopurine) • Corticosteroids • Vincristine • Cyclophosphamide • Anthracyclines • Asparaginase	• NHL specific protocols/regimens – LSA2L2 (ALL) – COMP – CHOP + 6MP + MTX (NHL 75)	Histology- and immunophenotype-directed therapy **Burkitt** CHOP HDMTX Ara-C Etoposide • Introduction of ifosfamide into BFM regimens **Lymphoblastic** • ALL-based treatment **Large cell** • CHOP/APO in U.S. • Immunophenotype-based (B- vs. T-cell) in Europe	**Burkitt** • Intensification of CTX and MTX (LMB-89) • Decreased intensity for Group B (LMB-89) **Lymphoblastic** • Intensified ALL regimen with prophylactic cranial RT (BFM90) **Large cell** • B-cell (as per Burkitt) • ALCL (as per Burkitt or CHOP/APO)	**Burkitt** • Intensive CTX-based with HDMTX/Ara-C **Lymphoblastic** • Intensive ALL based therapy **Large cell** • Immunophenotype-directed therapy (B- vs. T-cell)	Agents below are all still commonly used for NHL, but specific combinations vary based on histology • Cyclophosphamide • Doxorubicin • Vincristine • Prednisone • 6MP • Methotrexate • Ara-C • Asparaginase • Etoposide • Ifosfamide • Duration of therapy varies by histological subtype Burkitt/DLBCL: 3–8 months Lymphoblastic: 2–3 years ALCL: 4–12 months
Radiation therapy	Varied	Varied NHL75 randomized RT for advanced stage patients	• CNS prophylaxis with cranial RT for lymphoblastic • Elimination of IFRT in limited stage NHL	• Elimination of cranial RT for CNS + Burkitt/ B-ALL (LMB-96) • Elimination of prophylactic cranial RT (BFM 95)	• Radiation therapy limited to cases with relapsed/refractory disease	• Irradiation limited to cases with relapsed/refractory disease

ALCL, anaplastic large cell; ALL, acute lymphoblastic leukemia; APO, doxorubicin, vincristine, mercaptopurine, and prednisone; Ara-C, cytosine arabinoside; BFM, Berlin–Frankfurt–Münster; CHOP, cyclophosphamide, doxorubicin (Adriamycin), vincristine (Oncovin), and prednisone; COMP, cyclophosphamide, vincristine, methotrexate, prednisone; CTX, cyclophosphamide; DLBCL, diffuse large B-cell lymphoma (including mediastinal large B-cell lymphoma); HDMTX, high-dose methotrexate; IFRT, involved-field radiation; RT, radiation

COMP was found to be more effective for children with Burkitt lymphoma, whereas LSA2L2 resulted in a superior outcome for those with lymphoblastic lymphoma [75], and the importance of a histology-directed approach to treating pediatric NHL was recognized. Other significant observations during this period were made from the randomized study of CHOP (cyclophosphamide, hydroxydaunorubicin, vincristine, and prednisone), involved-field radiation therapy (IFRT) and CNS prophylaxis (cranial irradiation plus IT chemotherapy) in advanced stage patients, which showed no advantage for IFRT, but lower rates of CNS relapse with CNS prophylaxis [72].

In the 1970s and 1980s, standard treatment components for Burkitt lymphoma included cyclophosphamide, high-dose methotrexate, cytarabine, and intensive CNS prophylaxis, generally administered using short (4–9 months) intensive regimens, particularly for advanced-stage cases [76–81]. Some regimens also utilized etoposide. Pilot studies confirmed that the duration of therapy could be abbreviated for some groups [82,83]. Protocols for lymphoblastic lymphoma were typically based on intensive ALL treatment regimens that included intrathecal chemotherapy and/or cranial irradiation and an extended duration of antimetabolite maintenance (18 months to 3 years); high-dose methotrexate and etoposide were also included in some regimens [79,80,84,85]. Treatment for large cell lymphoma varied by continent with therapy determined by immunophenotype in Europe but not in the United States. Most protocols used CHOP or a CHOP-like regimen (e.g., doxorubicin, vincristine, mercaptopurine, and prednisone [APO]; or, cyclophosphamide, doxorubicin, vincristine, mercaptopurine, and prednisone [ACOP+]) [73,86]. A 1980s study established that IFRT could be safely withheld from the treatment of children with limited-stage NHL without compromising outcome [87].

In the 1990s, modulation of treatment intensity based on risk was evaluated to improve treatment outcome and reduce late effects. Most children with Burkitt lymphoma were eligible for regimens which further intensified therapy [88–92]. The LMB89 regimen included dosage escalation of cyclophosphamide, cytarabine and high-dose methotrexate, and cranial irradiation for those with CNS involvement [90]. Subsequently, the international collaborative B-cell study (LMB-96) demonstrated that dosage intensity could be safely reduced for some patients and that cranial irradiation could be safely eliminated for those with CNS disease at diagnosis [66,68]. Children with lymphoblastic lymphoma were eligible for intensive ALL-based regimens [69]. The BFM group reported outstanding results with an ALL-based regimen which included an induction/consolidation phase, followed by four courses of high-dose methotrexate given every other week, re-induction and maintenance; CNS prophylaxis included cranial radiation and intrathecal chemotherapy [69]. Later that decade, the BFM and others demonstrated that prophylactic cranial irradiation could be safely eliminated without compromising outcome [93,94]. Immunophenotype-directed treatment for children with large cell lymphoma eventually became the global standard. Those with B-cell large cell lymphoma were generally treated with Burkitt lymphoma regimens, whereas those with anaplastic large cell lymphoma were prescribed either APO or B-cell based BFM therapy [95,96]. APO incorporated a higher cumulative dose of anthracycline along with vincristine and prednisone while the BFM included additional agents (e.g., cyclophosphamide and methotrexate).

The outstanding improvements in treatment outcome for children with NHL achieved in the pre-2000 era can be attributed to the sequential refinement of risk-based, histology/immunophenotype-directed protocol therapy [66,68]. CHOP and modified CHOP-derivative regimens (APO and ACOP+) continue to be used, although the cumulative dosages of both doxorubicin and cyclophosphamide have been reduced for favorable risk patients to mitigate adverse effects. Ongoing trials using novel biologic agents aim to improve outcomes and reduce late treatment complications. Anti-CD20 has been studied in two international trials [97] and strategies for including anti-CD30 and/or small molecule inhibitors of anaplastic lymphoma kinase (ALK) in regimens for anaplastic large cell lymphoma are under consideration [98].

DISCUSSION

Notwithstanding the considerable therapeutic changes that have ensued over the last 50 years, this review clearly demonstrates that contemporary regimens for pediatric hematological malignancies continue to prescribe many of the same agents and modalities utilized in the treatment of historic cohorts. Corticosteroids and vinca alkaloids are still included in regimens for all of the common pediatric lymphoid malignancies. Antimetabolites including methotrexate, mercaptopurine and cytarabine remain essential components of ALL, AML, and NHL therapy. Monitoring of historic cohorts has established dose-related toxicity profiles for alkylators and anthracyclines, which has informed the risk-adapted use of these agents in present day protocols, as well as health counseling and surveillance of long-term survivors. Likewise, identification of chemotherapy schedules and combinations predisposing to epipodophyllotoxin-associated secondary AML has significantly influenced how etoposide is used in current practice.

In contrast, the use of radiation therapy has declined substantially, motivated by the recognition of long-term effects of radiation on normal tissues. These concerns led to the development of systemic and intrathecal chemotherapy regimens that are as effective as cranial irradiation in treating or preventing CNS disease in children with ALL, AML, and NHL. Combination chemotherapy concurrent with improved understanding of cancer biology ultimately resulted in abandonment of IFRT for local control of granulocytic sarcoma in AML and bulky nodal masses in NHL. Although radiation therapy remains an important modality in children with HL, most ongoing trials are focused on identifying patients who can achieve long-term survival without the use of this modality. For those who require irradiation, progress in radiation technology and delivery has facilitated better protection of normal tissues by conforming dose delivery to target volumes. However, correlation of the relationship of specific outcomes (e.g., breast cancer) with dosimetry from historic cohorts to target organs still provides useful information about very long-term health risks pertinent to contemporary treatment planning.

Monitoring of long-term survivors treated with agents and modalities with well-characterized toxicity remains important to determine how therapy modifications impact the prevalence and spectrum of late effects. For example, the increased use of dexamethasone in contemporary ALL therapy has resulted in a higher prevalence of osteonecrosis, and spurred research to identify clinical and genetic factors predisposing to this complication and its long-term functional implications [99]. Likewise, longer

follow-up is needed to establish if restricting cumulative anthracycline dose actually reduces the risk of cardiomyopathy or simply delays the time to onset of clinically symptomatic left ventricular systolic dysfunction [100].

While there is much commonality among historic and contemporary treatment approaches in their utilization of conventional chemotherapy and irradiation, investigations implemented in the last decade are novel in their aims to evaluate biological and targeted agents. Elucidation of the molecular changes that underlie cancer development has spurred the development of anti-cancer agents that target malfunctioning molecules and cellular pathways. While such targeted approaches offer the potential for more effective and rational cancer therapy, it is anticipated that these agents will likely, at least initially, be used in combination with conventional cytotoxic chemotherapy and radiation therapy. Moreover, there will likely be a slow trajectory of integration of such novel agents and technologies into contemporary regimens that are already highly effective. Therefore, demonstration of the long-term adverse effects of historical therapy will continue to play a crucial role in defining the optimal therapy for these diseases.

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