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REVIEW
Children's Oncology Group's 2013 Blueprint for Research: Non-Hodgkin Lymphoma

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on behalf of the COG Non-Hodgkin Lymphoma Committee

Non-Hodgkin lymphomas account for approximately 7% of cancers diagnosed in patients less than 20 years of age, with approximately 800 cases diagnosed annually at COG institutions. With current therapies, cure rates range from 70% to over 90%, even for children with disseminated disease. However, two major challenges need to be overcome: (i) to optimize upfront treatment to prevent relapse since prognosis for patients with relapsed disease remains poor and (ii) minimize long-term side effects in survivors. Hence, the future initiatives for the treatment of pediatric NHL are to utilize novel targeted therapies to not only improve outcomes but to decrease bystander organ toxicities and late effects. Pediatr Blood Cancer 2013;60:979–984. © 2012 Wiley Periodicals, Inc.

Key words: children; children's oncology group; lymphoma

INTRODUCTION

NHL accounts for approximately 7% of cancers in patients under 20 years, or approximately 800 cases annually amongst COG institutions. With current therapies based on histology, cure rates range from 70% to over 90%, even for disseminated disease. However, two major challenges remain and need to be overcome: (i) to optimize upfront treatment to prevent relapse since prognosis for patients with refractory of relapsed disease remains very poor and (ii) minimize long term side effects survivors. Therefore, a major objective for the pediatric NHL field is to utilize novel targeted therapies to not only improve outcomes for patients but also to decrease bystander organ toxicities and late effects.

STATE OF THE DISEASE—CLINICAL

Overview

Malignant lymphomas (Hodgkin and non-Hodgkin) are the third most common malignancy among children and adolescents. For pediatric NHL in the US, the estimated 5-year survival rates range from approximately 70% to >95%, depending on stage and histology. Unlike adult lymphomas, pediatric NHL more often presents as high-grade tumors with disseminated disease with extranodal involvement, requiring distinct treatment approaches. In children the median age at presentation is 10 years, while presentation below 3 years of age is infrequent. NHL has a male predominance and is almost twice as common in whites compared to African Americans. Specific populations at risk for NHL include those with congenital or acquired immunodeficiencies, including patients on immune suppression after transplant and HIV infection [2].

Current Outcomes

Lymphoblastic lymphoma (LBL). LBL therapy is based on ALL protocols that achieve survival rates of >90% for low-stage disease and >80% for advanced-stage disease [3]. CNS disease portends worse prognosis, but is less common in T-LBL than in T-ALL. COG demonstrated that minimal disseminated disease at diagnosis has prognostic value, as indicated by flow cytometric evidence of tumor cells in bone marrow [4]. Consequently, the COG now risk-stratifies patients with T-LBL based on the presence of minimal disease in the bone marrow at presentation. CNS prophylaxis is needed for LBL; however, chemotherapy is as effective as prophylactic cranial irradiation in CNS-negative patients, even with advanced-stage disease [5–8].

Burkitt lymphoma (BL). The overall survival for BL exceeds 85% irrespective of stage, except for patients with CNS involvement where event free survival is approximately 80% [9]. Poor prognostic features are high LDH at presentation, cytogenetic abnormalities such as 7q, 13q-, and partial duplication of 1q, and a suboptimal response to initial cytoreduction therapy. Completely resected, localized BL is curable with minimal therapy consisting of two courses of COPAD (cyclophosphamide, vincristine, prednisolone, and doxorubicin) without intrathecal chemotherapy with a 4 year OS of 99.2% [10]. Advanced stage BL, however, requires aggressive combination chemotherapy with CNS prophylaxis. High dose cyclophosphamide, methotrexate, cytarabine, and low-doses of anthracyclines are currently used, with or without epipodophyllotoxins. For intermediate-risk patients (group B) The French–American–British (FAB-96; CCG5961) study successfully reduced the cumulative dose of cyclophosphamide and omitted multi-agent maintenance cycle without compromising an EFS of 90% [11]. For high-risk (group C) patients EFS is 79–84%; however, a reduction in intensity and duration of therapy resulted in inferior outcome. This study confirmed that CNS radiation can be omitted for patients with CNS involvement at diagnosis without impacting the outcome.

Diffuse large B cell lymphoma (DLBCL). With current treatment children and young adults with Diffuse large B cell

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lymphoma (DLBCL) have a 5-year OS of 90%. In DLBCL, females, c-*myc* rearrangements, primary mediastinal B cell lymphoma (PMBL), and LDH of >500 U/L confers the poorer prognosis [12]. As opposed to adults with DLBCL, best results in pediatric DLBCL have been achieved using BL regimens [13]. Therefore, in pediatric DLBCL, treatment traditionally includes intrathecal chemotherapy for CNS prophylaxis. However, since CNS involvement is infrequent in DLBCL, it is unclear if intensive CNS-directed therapy is necessary [13,14].

Anaplastic large cell lymphoma. ALCL was first described in 1985 as a clinicopathologic variant of LCL [15]. ALCL are typically CD30+ and associated with chromosomal rearrangements involving a translocation which fuses the *NPM*, nucleolar phosphoprotein gene, on chromosome 5q35 with anaplastic lymphoma kinase (*ALK*), on chromosome 2p23. ALCL accounts for 8–13% of childhood NHL and 30–40% of pediatric LCL. Although bone marrow and central nervous system involvement is uncommon most have advanced disease at presentation. One-third present with localized disease [16]. The optimal treatment strategy remains to be defined, with survival ranges from 70% to 85%, regardless of treatment [17–19]. Vinblastine has been demonstrated to have significant activity in relapsed ALCL [1] and has been incorporated as front-line treatment into two randomized trials—a multi-national European trial (ALCL99) and in the APO (COG trial in the United States). The COG study ANHL0131 demonstrated no benefit of the addition of vinblastine [20]. In ALCL99, patients receiving vinblastine maintenance for 1 year had a better 1 year EFS (91%) than those without vinblastine (74%); however, the 2-year EFS fell to 73% for both groups [21]. Additionally, ALCL99 demonstrated, methotrexate given as 1 g/m^2 over 24 hours was comparable to 3 g/m^2 over 3 hour infusions without intrathecal chemotherapy, but the latter had less acute toxicity [22]. The remarkable activity and relatively little toxicity of brentuximab vedotin (tubulin-inhibitor conjugated monoclonal anti-CD30) and crizotinib (oral ALK inhibitor) in relapsed ALCL patients [23,24], has lead cooperative groups to pursue testing the efficacy and toxicity of adding these two biologic targeted agents with standard chemotherapy in newly diagnosed pediatric ALCL patients.

Post-transplant lymphoproliferative diseases (PTLD). PTLD are typically associated with Epstein–Barr virus (EBV) reactivation in organ or stem cell transplantation. Solid organ transplant (SOT) related PTLD is more common in children than in adults. In children, PTLD is typically of B-cell origin. In the USA, approximately 150 new cases of PTLD are diagnosed in children each year. These highly immunogenic tumors, amenable to immune based therapies, have Type III latency, where all latent EBV proteins are expressed. Many treatments for childhood PTLD have been explored but few multicenter collaborative studies are reported. Withdrawal or reduction of immunosuppression is a standard first approach for PTLD but success depends on whether the immune function recovers promptly enough to eradicate EBV-infected B cells. After SOT, radiotherapy or surgical resection for localized disease can achieve complete remissions [25]. In a study of children with PTLD that was refractory to reduction of immune suppression, six cycles of low dose cyclophosphamide and prednisone and six doses of rituximab (monoclonal anti-CD20 antibody) were given. The 2-year EFS and OS was 71% and 83%, respectively [25].

STATE OF THE DISEASE—BIOLOGICAL

Molecular Targeting of NHL Cells Using antibodies

Among the more studied antibody targets for NHL include the overexpression of CD20 or CD30.

CD20. Rituximab is a mouse/human chimeric monoclonal antibody targeting CD20 which is highly expressed in BL and DLBCL. In adults, the addition of rituximab to CHOP chemotherapy is beneficial for DLBCL [26,27] and can be given safely in combination with intensive BL therapy [28]. In children, single-agent rituximab showed activity for BL in a phase II window study for newly diagnosed patients [29]. Adult data suggest that rituximab may allow diminished use of agents with serious acute or late toxicities, warranting further study [27]. COG ANHL01P1 demonstrated the safety of adding rituximab to the FAB96 (CCG 5961) backbone [30]. Based on these results, the recently opened international collaborative study INT-B-NHL ritux 2010 (COG ANHL1131) will test the benefit of adding rituximab to the FAB96 backbone in high-risk pediatric BL and DLBCL in a randomized phase III study. Additionally, this study will test safety and efficacy of the DA-EPOCH-rituximab regimen [31] in pediatric PMBL in a phase II study.

CD30. Current studies in adults with ALCL suggest that CD30 can be targeted with the tubulin inhibitor conjugate anti-CD30 monoclonal antibody, brentuximab vedotin. The data in adults with relapsed ALCL demonstrate significant activity with relatively little toxicity [32]. Experience in combining brentuximab vedotin with chemotherapy is emerging and pediatric experience is limited. COG is pursuing studies to test safety and efficacy in combination with chemotherapy of brentuximab vedotin in CD30(+) lymphoma.

Targeting the ALK Pathway

In ALCL, the chromosome 5q35;2p23 translocation links the amino terminus of nucleophosmin (NPM) with the catalytic domain of ALK [33]. This oncogenic chimeric NPM-ALK protein is thought to trigger antiapoptotic signals via phosphatidylinositol 3-kinase/AKT and in conjunction with secondary molecular events leads to lymphoma. The remarkable activity and relatively little toxicity of brentuximab vedotin (tubulin-inhibitor conjugated monoclonal anti-CD30) and crizotinib (oral ALK inhibitor) [34] in relapsed ALCL patients [23,24], will lead COG to pursue testing the efficacy and toxicity of adding this two biologic targeted agents with standard chemotherapy in newly diagnosed pediatric ALCL patients.

EBV

In vitro EBV infected B lymphocytes transform into long-lived B lymphoblastoid cell lines (LCLs) expressing all nine latency-associated proteins. These type 3 latency cells are highly immunogenic, and are observed in EBV-associated lymphomas in individuals who are severely immunocompromised by organ transplantation (PTLD), HIV infection or immunodeficiency syndromes. Such tumors are usually well controlled by the adoptive transfer of EBV-specific cytotoxic T lymphocytes (EBV-CTL). EBV-CTL have been shown to be highly effective in EBV-associated lymphomas [35], but due to regulatory restrictions been limited to only a few centers. Nevertheless, several groups

both in Europe and the USA are now pursuing multicenter studies using adoptive EBV-CTL therapy in the treatment of EBV-associated PTLD in pediatrics.

CONCLUSIONS FROM RECENT STUDIES CONDUCTED BY COG FOR NHL

As discussed above, numerous advances have been made in the treatment of pediatric NHL both in Europe and in the USA over the past decade. Seven major studies have recently been completed by the children's oncology group and are highlighted as follows:

Pilot Study to evaluate the feasibility of adding rituximab to standard therapy for stage III/IV mature B-cell NHL. ANHL01P1 found no serious toxicities associated with rituximab infusion along with no unexpected increase in toxicity compared to chemotherapy alone. Rituximab pharmacokinetics found similar drug exposures to what has been observed in adult studies, with rituximab remaining detected in serum up to 6 months after last dose. The 3-year EFS rate was 93% (95% CI: 78–98%) for group B and 86% (95% CI: 70–94%) [30] for group C patients [36]. the study provided the key feasibility data for the current international intergroup study, INT-B-NHL ritux 2010 (COG ANHL1131).

Collaboration with the NCI Lymphoma SPECS project, to compare adult BL and DLBCL with pediatric BL/DLBCL. This study, found that compared with adult BL and DLBCL, the histologic diagnosis of pediatric DLBCL and BL is more likely (approximately 20–30% of cases) to be re-classified by molecular gene expression profile. Another finding was that in pediatric molecular DLBCL up to 75% of cases have over-expression of *c-MYC* by either translocation or gene gains or amplifications [37]. these data suggest that pediatric DLBCL usually has a more aggressive biology and provides justification for the use of BL regimens.

Phase II study adding rituximab to ifosfamide, carboplatin, etoposide or relapsed CD20+ pediatric lymphoma (ANHL0121). No significant toxicity was observed by adding rituximab to chemotherapy. CRs were observed in 3/6 patients with DLBCL and 4/14 patients with BL, with additional 5/14 PRs in BL patients. This regimen is now considered a standard of care for pediatric relapsed CD20+ lymphoma internationally [38].

Cooperative group trial for post-transplant lymphoproliferative disease. ANHL 0221 was a phase II study of a low-dose chemotherapy backbone (cyclophosphamide and prednisone) for six cycles plus weekly rituximab through first two cycles for progressive PTLD after solid organ transplantation. there was no increase in grade iii/iv toxicity observed for cycles with rituximab. The 2-year event-free survival (EFS) rate was 71% (95% CI: 57–82%) and 2-year overall survival (OS) rate for PTLD was 83% (95% CI: 69–91%). interestingly, neither histology, clonality, stage, early response nor response at end of therapy predicted outcome [25].

Using minimal marrow disease at diagnosis (MMD) to identify good-risk patients in T-cell lymphoblastic lymphoma. In 99 children with T-LBL treated on the COG a5971 study, 2-year EFS was 68 ± 11% for patients with >1% T-LBL cells in bone marrow by flow cytometry methods, as compared to 91 ± 4% for patients with <1% marrow involvement [4]. the open AALL0434 study is for T-cell LBL patients with disseminated disease and patients are risk stratified based on MDD at diagnosis.

Phase III study (ANHL0131) for advanced stage anaplastic large cell lymphoma comparing the efficacy of vinblastine versus vinblastine in maintenance. As discussed earlier, no difference was observed between the two arms and the study was closed early due to futility [20].

Randomized 2 × 2 factorial design study for patients with lymphoblastic lymphoma. The COG A5971 study was designed to determine: (a) the affect of induction intensification and (b) the best method for CNS prophylaxis (high-dose methotrexate in consolidation versus intrathecal methotrexate in maintenance). We found no benefit in outcome but increase toxicity with induction intensification and no difference in method of CNS prophylaxis [39]. This study also produced the largest series of pediatric patients with localized LBL and demonstrated excellent outcome with reduction of intrathecal treatments [40].

STRATEGIC APPROACH: TARGETED THERAPIES

Evaluating the Efficacy of Anti-CD20 Therapy for Pediatric Patients With Burkitt Lymphoma and Diffuse Large Cell Lymphoma

Rituximab in association with chemotherapy has become the standard treatment for DLBCL in adults. However, there are limited data for the use of rituximab in childhood B-cell lymphomas. Results from adult B-cell lymphoma cannot be assumed to apply to children because of differences in the biology of childhood DLBCL [37] and because >75% of childhood B-cell lymphoma are Burkitt lymphoma/leukemia, where efficacy of rituximab has never undergone evaluation in a prospective randomized trial (either in adults or children). Because EFS is already high in children with the current intensive chemotherapy regimen, and because rituximab is an expensive medication, which could produce potential severe side effects (e.g., prolonged lymphoid B cell depletion and infections), a large randomized trial is necessary to evaluate whether rituximab can add benefit to the current chemotherapy regimen. International collaboration is required to accrue sufficient number of patients in this population.

Exploring a New Therapeutic Approach for PMBL

Two pilot studies completed in children provide the preliminary evidence regarding the safety and activity of rituximab in B-cell malignancies. In FAB96 (CCG 5961) EFS for PBML was 70% and in the COG ANHL01P1, of the four patients with PMBL, two had recurrent disease, accounting for two of the three recurrences observed in the 45 group B patients. These results therefore suggested that the FAB96 backbone, even with addition of rituximab may not be optimal for this patient population. In an effort to maximize cure rates of B-cell malignancies, investigators have attempted to improve the therapeutic index of chemotherapy by taking advantage of increased sensitivity of highly proliferative tumors to prolonged exposure to low concentrations of chemotherapy. Based on data demonstrating decreased chemoresistance *in vitro* with low-dose, continuous administration of vincristine and doxorubicin, as well as synergistic effect of etoposide with CHOP, researchers at the National Cancer Institute initiated the dose-adjusted etoposide, prednisone, vincristine,

cyclophosphamide, doxorubicin (DA-EPOCH-R) regimen for adults with PMBL [41]. In this regimen, rituximab is given along with vincristine, doxorubicin, and etoposide which are administered as a continuous infusion over 4 days. Doses of doxorubicin, cyclophosphamide, and etoposide were increased by 20% per cycle until the patients experienced prolonged (>1 week) neutropenia or platelet count less than 25 × 10E9/L. This regimen showed a 100% OS and a PFS of >95% for adult patients with PMBL [41]. Based on these studies, the efficacy and tolerability of the DA-EPOCH-R regimen in children is currently being investigated in an international/intergroup trial (ANHL1131) as a separate arm for pediatric patients with PMBL.

Evaluating Targeted Therapies Using Small Molecules and Antibodies for the Treatment of ALCL

Despite numerous treatment strategies over the last 20 years for pediatric ALCL, relapse rates remain 25–30%. Hence the COG will explore two novel targeted therapies for the treatment of this disease. The hypotheses to be tested are: (i) that the novel antibody-drug conjugate brentuximab vedotin a tubulin inhibitor auristatin conjugated into a humanized monoclonal anti-CD30 antibody, given in combination with standard chemotherapy will be tolerable in pediatric ALCL and (ii) that the novel agent crizotinib, an oral small molecule inhibitor of the NPM-ALK fusion protein, given in combination with standard chemotherapy will be tolerable in pediatric ALCL. The results of this pilot study should allow the development of a follow-up trial which will test whether these agents can improve survival in pediatric ALCL. Moreover, the study aims to determine the prognostic significance of minimal disease at diagnosis and minimal residual disease as measured by RT-PCR in peripheral blood.

NHL Biology and Therapeutic Target Identification

Aggressive B-cell lymphomas. From the Phase 3 International Trial-ANHL1131 which will evaluate the potential prognostic value of minimal disseminated disease (MDD) and minimal residual disease (MRD) at time points during therapy to correlate with outcome, the MDD/MRD assay will be used as an assessment tool to identify response and efficacy of future targeted therapeutic agents. Additionally, as part of this international effort, groups in both Europe and the USA will also determine the molecular basis of pediatric Burkitt lymphoma, primary mediastinal B-cell lymphoma, and diffuse large B-cell lymphoma using high density SNP arrays on formalin fixed tissues and next generation sequencing technologies on available frozen tissues.

Anaplastic large cell lymphoma. Phosphoproteomic studies are aimed at identifying novel therapeutic targets in ALK positive ALCL. These studies have the potential to discover mechanisms of resistance to small molecular inhibitors of ALK or anti-CD30 (SGN-35) therapy. In the upcoming ALCL study, correlative biology studies will be performed to monitor NPM-ALK transcript levels in patients treated with crizotinib and SGN-35 as have been performed previously on other COG studies (e.g., ADVL0912).

PET and Minimal Residual Disease (MRD) as Prognostic Factors

In the ANHL1131 international trial, minimal residual disease will be measured after COPADM1 (only for B-AL patients and the same day as the PET(-CT) scan is performed) and at remission assessment time (post the first consolidation cycle). This will be performed using a highly sensitive PCR assays. The prognostic value of MRD in BM and PB before the second course will be evaluated in B-AL patients and the prognostic value of MRD in BM and PB at the remission assessment time will be evaluated in patients in clinically complete remission at that time.

T-Cell Immunotherapeutic Approaches for NHL

Adoptive immunotherapy has an established place in the treatment of viral infection and relapse after allogeneic hematopoietic stem cell (HSC) transplantation [42–46]. Ongoing studies are now exploring adoptive immunotherapy in relapsed low grade lymphoma after transplantation and EBV-associated malignancy [35,47]. In a three institution study of 114 patients, EBV-specific CTLs were infused to prevent or treat PTLD with minimal toxicity. Of 101 receiving CTL infusions as prophylaxis none developed PTLD. Of 13 patients treated for active disease, 11 achieved durable complete remissions, and no relapse. In solid organ transplant, in contrast to HSCT, PTLD usually arises in recipient B-cells and no HLA matched donor is usually accessible. In the absence of full matching between donor and recipient a partially matched donor T cells would need to be effective through a limited number of shared antigens. Alternatively, autologous T cells can be used and *in vivo* functionally active CTL have been successfully generated from patients on prolonged immunosuppression [48–51]. When autologous CTL were used pre-emptively, no patient developed PTLD. These studies allayed concerns that autologous EBV-specific CTL might induce rejection of the transplanted solid organ [48,49]. While EBV-specific T cell therapy is effective the approach is restricted by their patient-specific nature and limited availability. These constraints can be overcome by creation of a bank of HLA-typed EBV-specific T-cell lines. This third-party approach was tested by Haque et al. [52], who manufactured a bank of polyclonal EBV CTL lines to treat EBV-associated diseases in patients undergoing HSCT or solid organ transplantation. The lines were generated from blood donors and selection of the CTL were based primarily on the best HLA match [53]. In a phase II multicenter trial (19 transplant centers) for EBV positive PTLD not responding to conventional therapy, 33 patients received the best-HLA-matched ''off-the-shelf'' product [54]. Overall response rates were 64% at 5 weeks, and 52% at 6 months. Similar results have been reported from the UK and elsewhere in the USA [55–59]. Hence, this approach shows promise, and warrants further testing in definitive studies.

KEY CLINICAL TRIALS BEING PURSUED BY COG FOR PEDIATRIC NHL

Pivotal Phase 3 International Trial—ANHL1131

This international intergroup study involving groups from Europe, USA, Canada, and Australasia (AIEOP, BSPHO, DCOG, HSPHO, PPLLSG, SEHOP, SFCE, UK NCRI CCL CSG, and COG) is open to patients with advanced stage B-cell NHL (patients with stage III disease and LDH greater than two times normal and any patient with stage IV disease) or mature B-cell leukemia (>25% blasts in marrow) EXCLUDING patients with PMBL. The study aims to determine whether six infusions of

rituximab added to a standard intensive chemotherapy regimen (''LMB'' therapy) will improve the event free survival compared with the chemotherapy regimen alone. Children and adolescents with aggressive B-cell NHL currently have an event free survival rate of less than 90% with current therapy. Six hundred patients (40% from COG) from the nine international pediatric cancer cooperative groups will be accrued over 5 years to determine if rituximab reduces the risk of relapse by 50%. The secondary objectives of this study are to: (i) determine the effect of the intensive chemotherapy regimen with and without rituximab on immunoglobulin levels (and need for immunoglobulin infusions), B-cell counts, pre-existing vaccine titers and response to vaccination at 1 year post completion of therapy and (ii) evaluate the potential prognostic value of MDD and MRD at two time points during therapy in correlation with outcome and (iii) to evaluate feasibility and prognostic value of PET scans in childhood pediatric B-cell NHL.

Phase 2 Studies

ANHL12P1. For the treatment of pediatric patients with ALCL, the COG plans to determine the tolerability of brentuximab vedotin given in combination with standard chemotherapy (**ALCL99**) and to determine the tolerability of crizotinib given in combination with standard chemotherapy (ALCL99). Patients will be randomized to two arms: Arm A will add brentuximab vedotin to standard chemotherapy per ALCL99 (3 g/m^2 methotrexate and no intrathecal chemotherapy) and Arm B will add crizotinib to standard chemotherapy per ALCL99 (3 g/m^2 methotrexate and no intrathecal chemotherapy). This design will allow for the determination of toxicity and outcome of brentuximab vedotin and crizotinib with chemotherapy.

Development of a new PTLD study to incorporate T-cell therapies. To build on the success of the recently completed first cooperative group trial for post-transplant lymphoproliferative disease (**ANHL0221**) the COG proposes to evaluate the use of ''off the shelf'' third party allogeneic EBV-CTLs in combination with ANHL0221 chemotherapy. This would represent the first multicenter study of its kind combining low dose chemotherapy and antibody therapy with ''off the shelf'' antigen-specific T cell therapy for this disease.

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