# ADVANCES IN LLM

Current Developments in the Management of Leukemia, Lymphoma, and Myeloma

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## Rituximab as Therapy for Acute Lymphoblastic Leukemia

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**H&O** What is the current standard of care for patients with adult acute lymphoblastic leukemia (ALL)?

**DT** Frontline treatment approaches for newly diagnosed ALL have evolved from "one size fits all" chemotherapy regimens to subtype-oriented chemotherapy programs. The traditional risk factors that influence selection of therapy primarily include characteristics of the host, such as age, and features of the disease, such as lineage (T-lymphoblastic, B-lymphoblastic, or Burkitt-type [mature B-cell] ALL) and karyotype (eg, Philadelphia chromosome [Ph]).

For example, treatment of adolescents and young adults (AYA) with newly diagnosed ALL has been impacted dramatically by several retrospective analyses which show superior outcomes for pediatric ALL regimens as opposed to conventional adult ALL regimens (Table 1).[1-7] This may in part be related to higher dose intensity of the nonmyelosuppressive components of pediatric programs, such as vincristine, corticosteroids, and asparaginase. However, these findings may also be simply accounted for by age differences in the comparative cohorts; in some cases the median age was as much as 3 years apart. The optimal age cut off point which distinguishes the "younger" adult benefiting from a pediatric-like approach from an "older" adult likely to be intolerant of such therapy remains in flux, but appears to be around age 40–45 years, beyond which higher treatment-related mortality negates benefits of intensification.[8] Enrollment of younger adults with ALL into prospective clinical trials using pediatric regimens is therefore paramount in order to determine the best age-based chemotherapy approach.

With respect to targeted therapy, frontline chemotherapy regimens for Ph-positive ALL should now include a tyrosine kinase inhibitor (TKI).[9] The role of allogeneic stem cell transplantation (SCT) in first complete remission (CR) has to be redefined in the context of pediatric-based regimens for younger adults and second generation TKIs in Ph-positive ALL.

Newer lineage-specific frontline therapy approaches include incorporation of novel chemotherapeutics (such as nelarabine [Arranon, GlaxoSmithKline] for T-lymphoblastic leukemia/lymphoma) or monoclonal antibodies (such as rituximab [Rituxan, Genentech] for Burkitt leukemia/lymphoma or CD20-positive precursor B-lineage ALL). Table 2 provides an overview of the subtype-oriented regimens as applied to adolescents and adults with de novo ALL at our institution.

**H&O** Are there differences in outcomes for subsets of ALL? If so, what are the factors which account for these differences?

**DT** Survivorship in pediatric ALL now exceeds 80%. However, long-term overall survival (OS) outcomes for adults rarely exceed 40% except in cases where targeted therapy has been successfully incorporated into standard chemotherapy regimens (eg, 3-year OS rates improved from 15% to 55% with imatinib [Gleevec, Novartis] for Ph-positive ALL and from 53% to 80% with rituximab for Burkitt leukemia/lymphoma).[9,10] As I mentioned earlier, age is one of the most significant factors influencing outcome, related not only to differences in the biology of the disease, but also to tolerance (or intolerance) of chemotherapy. Older patients (at least age 55 or 60 years) fare poorly with standard frontline chemotherapy (except in the case of Burkitt ALL) owing to 1) higher rates of treatment-related morbidity and mortality and 2) adverse disease features (eg, higher likelihood of Ph). Novel lower intensity treatment programs that do not compromise efficacy are desperately needed for this group. With respect to disease subtypes, the subgroup of B-lineage ALL which harbors the t(4;11)(q21;q23) karyotypic abnormality involving the mixed leukemia lineage (MLL) proto-oncogene currently has the worst outcomse; relapse is nearly certain in the absence of high-dose cytarabine regimens followed by allogeneic SCT in first CR. Histone deacetylase inhibitors and hypomethylating agents target the effects of MLL;

**Table 1.** Studies of Pediatric-based Protocols for Adolescents and Adults With De Novo Acute Lymphoblastic Leukemia

| Country | Regimen | Age Range (years) [Median P, A] | # Patients | % CR | % EFS (years) |
|---|---|---|---|---|---|
| **Retrospective** | | | | | |
| United States[1] | CCG (P)<br>CALGB (A) | 16–20 [16, 19] | 197<br>124 | 90<br>90 | 63 (7)<br>34 (7) |
| France[2] | FRALLE93 (P)<br>LALA94 (A) | 15–20 [16, 18] | 77<br>100 | 94<br>83 | 67 (5)<br>41 (5) |
| Netherlands[3] | DCOG (P)<br>HOVON (A) | 15–18 [15, 17] | 47<br>44 | 98<br>91 | 69 (5)<br>34 (5) |
| Italy[4] | AIEOP (P)<br>GIMEMA (A) | 14–18 [15, 16] | 150<br>95 | 94<br>89 | 80 (2)<br>71 (2) |
| United Kingdom[5] | ALL97 (P)<br>UKALLXII/E2993 (A) | 15–17 [NR, NR] | 61<br>67 | 98<br>94 | 65 (5)<br>49 (5) |
| Finland[6] | NOPHO (P)<br>ALL (A) | 10–25 [13, 19] | 128<br>97 | 96<br>97 | 67 (5)<br>60 (5) |
| United States[7] | Hyper-CVAD (A)<br>(includes modified ± rituximab) | 13–21 [19] | 83 | 98 | 62 (4)<br>70 (4)* |
| **Prospective** | | | | | |
| United States[21,22] | DFCI 91-01, 9501<br>DFCI | 15–18<br>18–50 | 51<br>74 | 94<br>82 | 78 (5)<br>73 (2) |
| Spain[23] | PETHEMA ALL-96 | 15–18<br>19–30 | 35<br>46 | 94<br>100 | 60 (6)<br>63 (6) |
| France[8] | GRAALL-2003 | 15–45 | 172 | 95 | 58 (3.5) |
| Canada[24] | Modified DFCI | 18–60 | 85 | 89 | 63 (5)* |
| United States[25] | Augmented BFM | 12–40 | 48 | 98 | 82 (2)* |

A=adult; AIEOP=Associazione Italiana di Ematologia e Oncologia Pediatrica; ALL=acute lymphoblastic leukemia; BFM=Berlin-Frankfurt-Munster; CALGB=Cancer and Leukemia Group B; CCG=Children' s Cancer Group; CR=complete remission; DCOG=Dutch Childhood Oncology Group; DFCI=Dana-Farber Cancer Institute; EFS=event-free survival; FRALLE=French Acute Lymphoblastic. Leukaemia Group; GIMEMA=Gruppo Italiano Malattie e Matologiche dell'Adulto; GRAALL=Group for Research on Adult Acute Lymphoblastic Leukemia; LALA=Lymphoblastic Acute Leukemia in Adults; NOPHO=Nordic Society for Pediatric Hematology and Oncology; NR=not reported; P=pediatric; PETHEMA=Programa para el Estudio de la Terapéutica en Hemopatía Maligna.

*Denotes overall survival.

incorporation of these agents into frontline therapy might improve the outcome.

### H&O What is the role of rituximab in the treatment of B-lineage ALL? What was the rationale for incorporating it into chemotherapy?

**DT** Rituximab is a chimeric monoclonal antibody that modulates the CD20 receptor, thereby inducing antibody-dependent cytotoxicity, complement-dependent cytotoxicity (CDCC), and apoptosis. It was the first monoclonal antibody approved for the therapeutic treatment of malignancy. Its efficacy has been well-established in non-Hodgkin lymphoma (NHL) as monotherapy and in combination with chemotherapy. The favorable impact of incorporating rituximab into chemoimmunotherapy regimens in part relates to its synergism with various chemotherapeutics, which is particularly relevant for hematologic malignancies such as chronic lymphocytic leukemia (CLL) where CD20 expression of the malignant clone is lower than that of normal B lymphocytes.

Whereas nearly all cases (80–90%) of mature B-cell or Burkitt-type ALL express high levels of CD20, in precursor B-lineage ALL, the corresponding rates range from 40–50% with varying levels of CD20 intensity. The prognostic significance of CD20 expression was first

**Table 2.** Current Frontline Chemotherapy Regimens for Adult ALL at M.D. Anderson Cancer Center

| Feature | Age Category (yrs) | Regimen |
|---|---|---|
| T-lymphoblastic | <30<br>>30 | Augmented BFM[25]<br>Modified hyper-CVAD + nelarabine[26] |
| B-lymphoblastic, Ph negative | <30<br>>30 | Augmented BFM[25]<br>Modified hyper-CVAD ± rituximab*[14] |
| B-lymphoblastic, Ph positive | All | Hyper-CVAD + dasatinib ± rituximab*[27] |
| Burkitt-type (mature B-cell) | All | Hyper-CVAD + rituximab[10] |

BFM=Berlin-Frankfurt-Munster; CVAD=cyclophosphamide, vincristine, doxorubicin, dexamethasone; Ph=Philadelphia chromosome.

*Rituximab is administered if CD20 expression is at least 20%.

evaluated in pediatric ALL with conflicting results.[11,12] We then evaluated the relevance of CD20 expression (defined as at least 20%) in 253 adolescents and adults with de novo B-lymphoblastic ALL treated with either conventional VAD (vincristine, doxorubicin, dexamethasone) or intensive hyper-CVAD (hyperfractionated cyclophosphamide, VAD) frontline therapy regimens in the pre-rituximab era.[13] CD20 expression was associated with worse outcomes (higher relapse rates and lower 3-year rates of CR duration and OS despite similar CR rates), particularly for the hyper-CVAD regimen. The adverse effect of CD20 expression on outcome was most pronounced in the younger subgroups (<60 years old).

Rituximab was therefore incorporated into the hyper-CVAD regimen at our institution for Burkitt-type leukemia/lymphoma in an attempt to mimic the success observed in elderly patients with NHL, and for CD20-positive B-lymphoblastic leukemia in an attempt to reverse the negative influence of CD20 expression on outcome.[10,14]

## H&O What do we know about the efficacy and safety of rituximab in the treatment of ALL?

**DT** Rituximab was incorporated into a modified hyper-CVAD regimen for newly diagnosed CD20-positive B-lymphoblastic leukemia.[7,14,15] Although CR rates were similar, the addition of rituximab improved the 3-year CR duration and OS rates for adolescents and younger adults (<60 years old) compared with the historical experience (from 28% to 68%, $P$<.001; and from 35% to 68%, $P$=.01; respectively). Unfortunately, there was no apparent benefit for the older group, in part related to a higher rate of deaths in CR observed early in the course of accrual related to complications of multidrug resistant bacterial infections prior to implementation of rotating antibiotic prophylaxis. This was in sharp contrast to the experience with Burkitt leukemia/lymphoma, in which the addition of rituximab to hyper-CVAD improved 3-year OS rates from 17% to 80% for the older group.[10]

In the German Multicenter Study Group for Adult ALL (GMALL) study 07/2003, younger patients with CD20-positive B-lymphoblastic leukemia were treated with rituximab according to risk group. For standard risk ALL, the addition of rituximab improved the molecular CR rates (from 57% to 89% at week 16) in addition to the 3-year rates of CR duration (from 48% to 64%, $P$=.009) and OS (from 54% to 75%). Similar improvements in outcome observed for the high-risk group treated with rituximab (OS rate increased from 40% to 75%) were attributed to reductions in relapses after allogeneic SCT.[16] In the younger patients treated with modified hyper-CVAD and rituximab at our institution and per the GMALL study 07/2003, there were no significant differences in rates of deaths in CR with the immunotherapy.

With respect to the safety of incorporating rituximab into chemotherapy regimens for B-lineage ALL, there does not appear to be any significant difference in the spectrum of toxicities when compared with chemotherapy alone. Of course, this does not mitigate the need for vigilance regarding known complications of rituximab-based therapy such as tumor lysis syndrome, reactivation of hepatitis B leading to fulminant hepatic failure, and development of fatal progressive multifocal leukoencephalopathy related to the JC polyomavirus.[17]

## H&O What are the remaining challenges in the treatment of ALL? What research is needed to overcome these challenges?

**DT** The key to improving the prognosis of ALL, particularly for adults, will be to further define the biologic subtypes that are amenable to incorporation of other novel targeted agents into the chemotherapy program. The next steps could include incorporation of rituximab into pediatric regimens for AYAs with CD20-positive B-lineage ALL, based on the positive experience I detailed earlier. In addition, there are pediatric data suggesting that CD20 expression is upregulated during induction chemotherapy, even in cases deemed CD20-negative at baseline. Rituximab could therefore conceivably become part of all frontline chemotherapy programs for B-lymphoblastic leukemia/lymphoma regardless of baseline CD20 expression.[15]

In adult ALL, continued development of more effective and novel therapeutics that either target or circumvent mechanisms of resistance will be paramount in order to

attain the success achieved in pediatric ALL. An example is the second generation anti-CD20 monoclonal antibody ofatumumab (Arzerra, GlaxoSmithKline), which binds to a different epitope on CD20 and has a superior CDCC effect compared with rituximab.[18] Incorporation of other monoclonal antibodies (eg, epratuzumab [LymphoCide, Immunomedics] or alemtuzumab [Campath, Genzyme] for CD22 or CD52 expression, respectively) into adult chemotherapy regimens is being explored. Another class of immunotherapeutic agents that appears promising include bispecific antibodies such as the anti-CD19 antibody blinatumomab, which utilizes bispecific T-cell engager (BiTE) technology to recruit effector T-cells and elicit an immune-mediated anti-leukemia response.[19] In vitro synergism of blinatumomab with rituximab has also been reported.[20]

Other targeted agents that should be explored include those that not only counter mechanisms of resistance to immunotherapy with rituximab, but also those that target various pathways involved in resistance of lymphoblasts to chemotherapy. Examples include hypomethylating agents that target methylation of relevant genes (eg, MLL and others), anti-Bcl-2 agents that target apoptosis, and mammalian target of rapamycin (mTOR) inhibitors which target the P13K/Akt survival pathway. Future research regarding pathophysiologic mechanisms of resistance in ALL should also focus on the interactions of lymphoblasts with their marrow microenvironment by using agents that exploit them (eg, inhibitors of the chemokine receptor CXCR4 and hypoxia-activated prodrugs). It is only by carefully elucidating all of the mechanisms that promote lymphoblast survival that the concept of personalized therapy of adult ALL will be realized, via administration of a tailored multi-targeted chemotherapy-based "cocktail" designed to attack all of the leukemia subclones that eventually would otherwise re-emerge.

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