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Targeting subtype in ALL - Section 18

Opportunities and challenges of personalized therapy of patients with HR ALL

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Take home messages

- **The opportunities:** Novel genomic diagnostics and availability of multiple new drugs create opportunities for personalized adjustment of therapy for HR ALL patients.
- **The major challenges:** Lack of reliable efficacy data and of specific clinical trials.
- **Recommendations:** Be conservative - minimize deviations from clinical protocols; Whenever possible enroll the patient in a specific clinical trial for the novel therapy; If not available– maximize local and central prospective collection of clinical and biological data on each patient.

Introduction

We are at the beginning of a new era in the treatment of children with ALL. Carefully conducted large cooperative clinical trials have achieved a remarkable success, with cure of most children with ALL. Curing every child with ALL with a much less toxic therapy may be achievable over the next decades. This goal may be achieved through personalized precision therapy. As "state of the art" data is lacking for this specific topic, my goal is to initiate discussion and enrich the awareness of physicians to the opportunities and challenges of personalized adjustment of therapy.

State of the art

Opportunities and challenges

Due to "next generation" genomic sequencing (NGS) methodologies we now know that ALL is a highly heterogeneous disease consisting of many genetic subtypes.[*1,2] Furthermore, each patient's ALL consists of multiple subclones that must be eliminated for cure.[*3,4] We also face a large plethora of therapeutic agents. One group consists of immunotherapeutic agents targeting the B cell phenotype and is thus (probably) agnostic to specific genetic abnormalities. The other consists of drugs blocking the activity of specific proteins essential for the growth and survival of the leukemic cells. Novel methodologies to test drug sensitivity of ALL have also been developed.[5] These advances in diagnostics and therapeutics enhance the opportunities for precise personalized adjustment of therapy. However, they also create unprecedented challenges for informed therapeutic decisions and for designing appropriate clinical trials (Table 1). These challenges are general for studying the efficacy of specific drugs for rare cancers.[6]

This lack of knowledge regarding the true efficacy of novel drugs is further affected by the popular scientific and general media. Scientific publications are skewed toward the publication of positive results. Negative observations are generally not published. Scientific progress, both in diagnostics and therapies, is further enhanced by popular media reports on spectacular cures. Commercial interests feed these reports. For example, various NGS diagnostic tests are heavily marketed to both patients and physicians. Altogether, this creates a serious pressure on treating physicians to deviate from clinical protocols and to apply a novel personalized therapy, often without sufficient knowledge on how "precise" and effective this therapy is compared with the approach of the clinical protocol in which the patient is treated.

Ph-like ALL as an example

Targeted therapy with BCR-ABL1 inhibitors has revolutionized the treatment of chronic myeloid leukemia (CML). Randomized clinical studies have demonstrated that the addition of imatinib to chemotherapy significantly enhances cure of BCR-ABL1 ALL.[7,8] It has also been recently shown, however, that TKIs markedly enhance treatment- related mortality of HR chemotherapy.[*9]

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Table 1

Opportunities and Challenges for precision personalized therapy of children with high risk ALL.

Opportunities	Challenges
Targetable genomic aberrations (e.g., Kinases)	Multiple genetic subtypes of ALL
Novel targeting drugs (e.g., kinase inhibitors)	High genomic heterogeneity – most genomic aberrations are subclonal
Immunotherapies (antibodies, CAR-T cells)	Rare patients – less than 10% of ALLs relapse
Availability of genomic diagnostic tests	Few clinical trials with novel agents
	Unknown efficacy of novel therapies
	Outcomes of personalized treated patients are not reported

Ph-like ALLs are a recently discovered of HR ALLs that are characterized by a similar gene expression to BCR-ABL1 ALLs.[*10] Genomic analysis has revealed two major groups of these leukemias – the minority (about 10% of all Ph-like ALL) in which the ABL1 signaling pathway is activated, and the majority, in which the genomic lesions are mainly in the JAK-STAT pathway.[11]

Many contemporary ALL clinical trials (except AIEOP-BFM) have decided to add TKIs to all patients with ABL-class mutations especially for patients with high levels of MRD at the end of induction. This "consensus" is based on biological studies displaying the similarity between BCR-ABL1 and ABL like ALLs and few clinical reports of individual cases (especially of EBF1-PDGFRB ALL, which is the most common abnormality comprising up to 1% of "B others" ALL).[12–15,*16,17]

The largest subgroup of Ph-like ALLs is characterized by genetic activation of the JAK-STAT pathway. The most common subtype consists of aberrant expression of CRLF2.[18] Currently, children in the USA with JAK-STAT ALLs are enrolled in a COG clinical trial in which ruxolitinib, a JAK1/JAK2 inhibitor, is added to chemotherapy (clinicaltrials.gov NCT 01164163). Unfortunately, this trial is not randomized. Efficacy will be judged compared with historical controls only. We have recently shown that in relapsed CRLF2 positive ALL, the JAK2 mutated clones often disappear and are replaced by RAS mutated cells. Furthermore, we observed a paradoxical enhancement of the survival of JAK2 mutated B cell leukemic cells treated with low dose ruxolitinib in-vitro at a concentration that is equivalent to the trough levels in children treated in the trial. These observations cast doubts regarding the potential role of JAK1/JAK2 inhibition in treatment of CRLF2 ALLs.

Rarely mutational activation of other kinases is observed in "Ph-like" ALL. NTRK fusions activating the TRK tyrosine kinases are extremely rare in hematological malignancies.[*10,*19,20] Recently, larotrectinib, a highly potent and specific TRK inhibitor, has demonstrated long term remissions in about 90% of children and adults with solid tumors harboring NTRK fusions.[21,22] Remarkably, based only on phase II trials, the drug was approved by the FDA for treatment of any tumor with NTRK fusion regardless of histology. Taylor et al treated one patient with AML and NTRK2 fusion with larotrectinib.[*19] The patient had a transient response. By this carefully conducted "single patient clinical trial" Taylor et al showed that larotrectinib is highly effective against leukemic cells with NTRK2 fusions. Yet, it did not help the patient because the fusion was present only in a subclone and not in all the cells. Hence when deciding if to apply a targeted therapy based on genomic analysis it is critical to know if the target is clonal (ie, present in all leukemic cells) or subclonal. Treatment is likely to be effective when directed at a clonal aberration.

Future perspective

The major challenge is how to appropriately/best apply novel therapy to HR ALL (and indeed to any high risk, highly curable, pediatric cancer). For many of these drugs conventional phase II/III clinical trials are unlikely. In general, I suggest being conservative – have a very strong case to apply novel therapies. If possible, patients should be enrolled on phase I/II clinical protocols. Regarding Ph-like ALL, I would add TKI to any ABL like ALL with positive MRD at the end of induction but would not treat with JAK inhibitors any of the CRLF2 ALL until the publication of the results of the current trial. I would consider alternative therapies (eg, immunotherapies) to any patient with highly refractory ALL or with serious toxicities that preclude further administration of high-dose chemotherapy.

What is critically important is to prospectively and actively collect information. The treating physician should collect biological specimens to allow future studies, similar to that performed by Taylor et al.[*19] Moreover, large phase III clinical trials of ALL should prospectively identify and collect detailed data on patients who deviate from the protocols by receiving an alternative "personalized" therapy. Such an approach is likely to reveal the true efficacy of a personalized approach with novel drugs to rare patients.

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