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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Immunotherapies (antibodies, CAR-T cells) Rare patients

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Table 1

| 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                                     |

Ph-like ALLs are a recently discovered of HR ALLs that are characterized by a similar gene expression to BCR-ABL1 ALLs. 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.

Many contemporary ALL clinical trials (except AIEOP-BFM) have decided to add TKIs to all patients with ABL1-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).

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. 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.

The most recent comprehensive genomic investigation uncovering multiple genetic subtypes of B-cell precursor ALL. The treating physician should collect biological specimens to allow future studies, similar to that performed by Taylor et al. 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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