Integration of MRD and Genetics as a Therapeutic Guidepost in ALL

Anthony Moorman
Newcastle University, United Kingdom

The outcome of children and adolescents with ALL has improved dramatically over the past 50 years and >90% patients treated on modern protocols will be cured. The advances driving this increase have been largely protocol refinement coupled with risk stratification alongside improved supportive care rather than new drugs. ALL is a heterogeneous disease with respect to demographics, presenting clinical features, cell of origin, underlying somatic genetic abnormalities and response to therapy. The structure of modern regimens emerged in the 1980s and gave rise to protocols comprising four phases - induction, consolidation, intensification and maintenance. Initial risk algorithms sought to identify patients with a higher-than-average risk of relapse and assign them to more intensive chemotherapy, directed therapy, longer maintenance therapy, a stem cell transplant or, occasionally, separate protocols. More recently, clinical study groups have started to employ risk stratification algorithms to identify lower risk patients with a view to de-escalating therapy. Broadly speaking risk stratification occurs at the protocol level and then again the risk group level. Whilst the vast majority of patients with ALL receive treatment on all-encompassing protocols, some patients with specific demographic or disease characteristics assigned to specialised protocols. Additional risk factors such as genetics and treatment response allocate patients into different treatment groups. Many treatment protocols enrol children and young adults and have observed the frequency of high-risk features (e.g. genetics) increasing with age. Initial studies indicate the most prognostic effect of many risk factors are age-independent.

The principal advances in risk stratification have emerged from incorporating and then integrating treatment response and genomic abnormalities. Response to initial therapy is an important risk factor and virtually all modern protocols assess the level of disease during treatment and assign slow responders to receive intensive chemotherapy. Historically, response was measured crudely by morphology after one or two weeks of therapy. However, the advent of minimal/measureable residual disease (MRD) techniques has revolutionised risk stratification by enabling the detection of very low levels of disease. Although MRD can be measured at any time-point, the end of induction is the most widely used time-point and 0.01% is the gold standard threshold for distinguishing between MRD positive and negative patients. Several studies have now demonstrated improved outcome for patients by either augmenting therapy for MRD positive patients or de-escalating therapy for MRD negative patients.

Despite the vast array of somatic genetic/genomic abnormalities identified and linked with prognosis, only a handful are used currently to risk stratify patients to specific treatments or therapeutic pathways. Childhood and adults patients with *BCR::ABL1*, and increasingly ABL-class fusions, receive tyrosine kinase inhibitors in addition of standard chemotherapy. While this targeted intervention improves, outcome additional risk factors (e.g. *IKZF1* deletions) are still relevant in these patients. The majority of modern paediatric protocols will assign patients with the classic high-risk genetic abnormalities [*KMT2A* fusions, near haploidy (<30 chromosomes), low hypodiploidy (30-39 chromosomes), *TCF3::HLF* or iAMP21] to the high-risk arm of the trial which will include more intensive chemotherapy and often a stem-cell transplant; or for the very high risk cases CAR-T cell therapy. The prognostic impact of the genomic subtypes such as *CRLF2*-rearrangements, *PAX5* P80R, *IKZF1* N159Y, *PAX5*-altered, as well as *MEF2D*- and *ZNF384*-rearranged cases is less well established in paediatric although some study groups do assign selected patients (e.g. *CRLF2*, *EPOR* and *JAK2* rearrangements) to receive targeted therapy. *ETV6::RUNX1* and high hyperdiploidy have been linked with an excellent outcome are increasingly being used to stratify patients to lower intensity treatment.

However, it should be noted that the definition of "low risk" high hyperdiploid is variable with some groups using the traditional chromosome number range of 51-67 chromosomes and others using the pattern of chromosome gain (e.g. triple trisomy, UKALL HeH profile).

There is more variability in the list of high-risk abnormalities in adult ALL, but the majority include *KMT2A::AFF1* fusion, low hypodiploidy, and complex karyotype; with some adding t(1;19)(q23;p13)/*TCF3::PBX1*. More recently, abnormalities leading to deregulated JAK-STAT signalling JAK-STAT abnormalities [*IGH::CRLF2, P2RY8::CRLF2* and *JAK2* fusions] have been linked with a very poor outcome.

More recently, the prognostic effect of secondary genomic lesions – typically deletions and deletion/mutation profiles – have been recognised and incorporated into risk algorithms. However, there is no standard approach and study groups have opted for different interventions for the same abnormality, e.g. *IKZF1* deletion. Some study groups have opted to use deletion profiles to identify risk groups and alter therapy but again there are differences in definition and approach. The BFM-AEIOP group have opted to use CNA to identify high risk patients via the IKZF1plus profile while the ALLTogether consortium is focussing on identifying low risk patients using the UKALL-CNA profile. In adult ALL, the prognostic impact of *IKZF1* deletions is more controversial. Whilst a few protocols have reported a prognostic impact of *IKZF1* deletions and implemented a treatment change other studies have reported no adverse effect.

MRD is widely recognised to be the single most powerful prognostic factor in paediatric and adult ALL. However MRD alone is not sufficient to predict outcome. Recent studies have shown that the prognostic effect of MRD is modulated by the genetic make-up of the leukemic clone and that the prognostic effect of some genetic abnormalities varies by MRD risk group. As a result, risk algorithms integrating risk factors have emerged. For example, the current DCOG trial and AEIOP-BFM-ALL2017 combine genetics and MRD to stratify patients: medium risk MRD patients with IKZF1 deletion and MRD positive patients with IKZF1plus, respectively. Analysis of data from UKALL2003 demonstrated that patients with good risk cytogenetics and MRD one log higher than the standard threshold had an excellent outcome and did not benefit from augmented therapy. Therefore, using a single timepoint and a single threshold to assign risk is an over-simplification which can lead to patients being either over- or under-treated. Statistical modelling of large well characterised patient cohorts has revealed that using subtype specific MRD thresholds can improved risk prediction. Moreover, fully integrating multiple risk factors into a single prognostic index can help to define risk groups which are more flexible than those generated by the sequential application of binary cut-points.

In conclusion, risk stratification in ALL has advanced massively over the past few decades and helped improve cure rates. Now the focus of risk stratification needs to switch from identifying high-risk patients to those patients curable with minimal chemotherapy thereby reducing long-term toxicity. The next wave of risk algorithms should integrate multiple factors and be flexible enough to support the design of innovative clinical trials including those that incorporate novel therapies e.g. immunotherapy.