# A post-stem cell transplant risk score for Philadelphia-negative acute lymphoblastic leukemia

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Recent decades have seen major advances in understanding the genetic basis of hematologic and non-hematologic malignancies. The discovery of the Philadelphia chromosome (Ph) in chronic myeloid leukemia was a key step forward.[1,2] Since then, many recurrent chromosomal abnormalities, such as t(8,21) and t(15;17), have been found in acute leukemias, paving the way for identification of altered genes.[3] These ongoing discoveries have provided and continue to provide major insights into the mechanisms by which key transcription factors and epigenetic modulators regulate normal hematopoiesis and, if dysregulated, promote leukemic transformation. To date, more than 200 balanced chromosomal rearrangements (translocations, insertions and inversions) defining biologically distinct subsets of acute leukemia have been identified. Chromosome analysis, together with molecular determinations, are now important components of routine clinical practice and essential for appropriate diagnosis. Cytogenetic findings have in addition been repeatedly shown to be among the most important and independent prognostic factors in both acute myeloid leukemia and acute lymphoblastic leukemia (ALL).[4,5] For all these reasons, specific chromosome alterations and their molecular counterparts have been included in the World Health Organization classification of hematologic malignancies and together with morphology, immunophenotype and clinical features are used to define distinct disease entities.[6]

The first comprehensive cytogenetic analysis showing biological and prognostic significance in adult ALL was performed at the Third International Workshop on Chromosomes in Leukemia in 1981.[7] The frequency of abnormal karyotypes was shown to be slightly higher in adult than in pediatric ALL (60-69% *vs.* 58-64%, respectively) with t(9;22)(q34;q11) being the most frequent translocation.[8] Less than 6% of children, but up to 40% of adults ≥40 years of age, with ALL harbor a Ph translocation ($Ph^+$) with or without additional alterations, which is a poor prognostic feature regardless of age. In contrast, less than 12% of adults, but 25% of children have high hyperdiploidy, a good prognostic feature.[4]

One of the hurdles to developing a more sophisticated cytogenetic profile is the overall incidence and, in particular, the different subsets of $Ph^-$ adult ALL, each of which accounts for less than 10% of the total. Only sparse information is available on $Ph^-$ ALL patients. The most frequent $Ph^-$ chromosomal aberrations include t(4;11)(q21;q23)/*KMT2A-AFFI* (3-7%) involving the *MLL* gene, translocations t(8;14)(q24;q11) (2%) involving *myc*, t(1;19)(q23;p13)/*TCF3-PBX1* (2-3%), t(10;14)(q24;q11) (2%), t(11;19)(q23;13.3) and structural abnormalities such as 9p, 6q, and 12p, 18, 19. Further cytogenetic changes include the multiaberrant karyotype, monosomy 7, monosomy 9, +8, del11 and low hypodiploidy, near triploidy and high hyperdiploidy. ALL study groups, including the Medical Research Council (MRC), Eastern Cooperative Oncology Group (ECOG), Southwest Oncology Group (SWOG), Northern Italy Leukemia Group (NILG), North UK and *Gruppo Italiano Malattie Ematologiche dell'Adulto* (GIMEMA) categorize the cytogenetic alterations at diagnosis into risk groups. Unfortunately, the representation of patients treated with hematopoietic stem cell transplantation (SCT) is limited in these analyses. The largest study with patients undergoing allogeneic SCT was the MRC-ECOG study with 310 patients.[9] Here, four risk categories were identified using the modified MRC-ECOG score (very high, high, intermediate and standard).[10]

In a study reported by Aleksandr Lazaryan *et al.* in this issue of *Haematologica*, the Acute Leukemia Working Committee of the Center for International Blood and Marrow Transplant Research (CIBMTR) investigated the usefulness of the MRC-ECOG score in a large cohort of patients after SCT (n=1731) all of whom were adults with $Ph^-$ ALL.[11] While the standard- risk group had favorable outcomes compared to the intermediate-risk group, the adverse risk group was not clearly inferior using the modified MRC-ECOG score. The analysis of relapse and post-transplant treatment failure revealed that t(8;14), monosomy 7 and complex karyotype were the major important determinants. As a consequence, the authors propose, in addition to the modified MRC-ECOG score at diagnosis, the CIBMTR risk score for transplant, which does not include the t(4;11), t(1;19), t(17;19), t(5;14) and +8, but does include t(8;14), t(11;19), monosomy 7, del(7q), del(11q) and complex karyotype (Figure 1).

Previous studies on ALL patients after SCT have concluded that cytogenetics do not predict overall survival. The difference in respect to the current study might be explained by the high number of patients transplanted in advanced phase disease in addition to the high number of patients with $Ph^+$ ALL included in one study.[12] Another study found no difference in overall survival between patients with high risk [defined as t(4;11)(q21;q23), t(8;14)(q24;32), low hypodiploidy, complex karyotype] and standard-risk cytogenetics, most probably as a consequence of the low number of patients in the high-risk group.[13] A different study identified t(4;11)/*KMT2A-AFF1* and t(v;14q32)/*IGH* in $Ph^-$ patients, but censored patients at the time of SCT.[14]

A source of uncertainty in the current analysis is the lack of information on cytogenetic results at transplant.[15] Furthermore, molecular information at diagnosis and minimal residual disease might have influenced the results of this retrospective analysis. Despite these flaws, the results

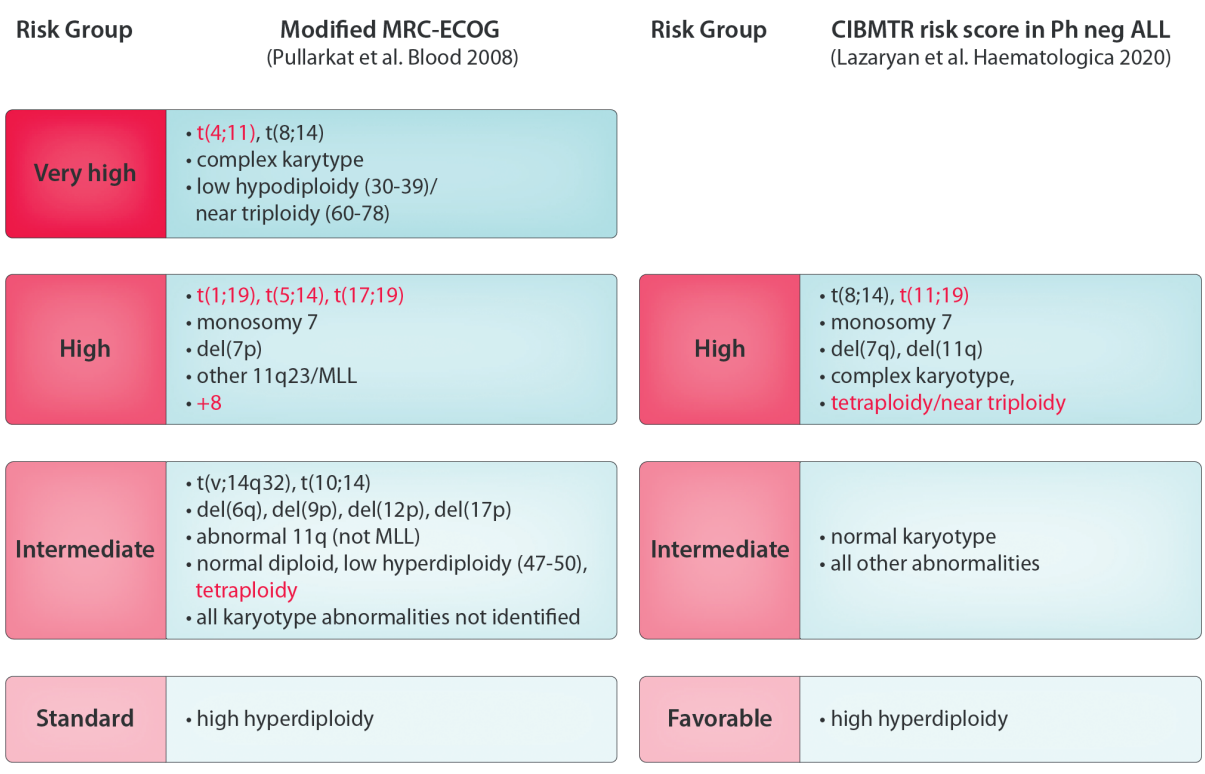


**Figure 1. Comparison of two cytogenetic risk classifications for Philadelphia chromosome-negative acute lymphoblastic leukemia.** The modified Medical Research Council – Eastern Cooperative Oncology Group (MRC-ECOG) score at diagnosis *versus* the Center for International Blood and Marrow Transplant Research (CIBMTR) risk score for post-transplant Philadelphia chromosome-negative acute lymphoblastic leukemia. Differences between the risk scores are shown in red.

are derived from the largest cohort of Ph$^-$ patients treated with SCT to date and show clear distinctions in leukemia-free survival (LFS) using just three risk groups.

Several aspects of the article by Lazaryan *et al.*[11] are of interest. Post-transplant risk scores differ from those for patients treated with conventional therapy. This may be a consequence of graft-*versus*-tumor susceptibility. It is interesting to see that translocations, except for t(8;14) and t(1;19), are noticeably absent from the CIBMTR risk score compared to the modified MRC-ECOG risk score (Figure 1). While t(1;19)(q23;p13), t(4;11)(q21;q23), t(5;14)(q35;q32) and t(17;19)(q22;p13) were identified as risk factors at diagnosis/before SCT, they were not considered to be adverse post-SCT. It is feasible that the abnormal proteins produced by translocations may directly or indirectly affect malignant cell immunogenicity and enhance the graft-*versus*-tumor effect.

The translocations t(8;14) and t(11;19) still remain in the high-risk category. A possible reason might be the association of t(8;14) with the involvement of the *myc* gene on chromosome 8 and of t(11;19) with the *MLL* gene, underlying the prevalence of tumor-specific rather than immunogenic factors.

Multiple mechanisms have been proposed to be responsible for the high relapse rate in diseases with monosomy 7 and complex karyotype, including loss of tumor suppressor genes, haplo-insufficiency or loss of *IKZF1*. These alterations may be less susceptible to graft-*versus*-tumor reactions. The results are similar to those previously seen in acute myeloid leukemia, in which t(11;19),[16-18] monosomy 7, deletion 7q[19,20] and complex karyotype are also risk factors and play an important role in outcome. Similar mechanisms might therefore influence relapse rates after SCT in both acute myeloid leukemia and ALL.

A further consequence of the results of the analysis by Lazaryan *et al.* is the evident need to reduce the relapse rate in high-risk (but also in normal-risk) patients. This may be possible by evaluating minimal residual disease before and after SCT. The important role of minimal residual disease in predicting outcome at an individual level has recently been published.[21] Optimizing SCT outcome by tailoring immunosuppression in the early phase, in response to post-transplant monitoring of disease-specific minimal residual disease or chimerism would be an appropriate approach. The relapse risk in Ph$^-$ ALL may be reduced by new drugs, such as blinatumomab, inotuzumab ozogamycin or tisagenlecleucel. In this context, the results presented by Lazaryan *et al.* should provide a stimulus for prospective clinical studies.

Furthermore, those translocations associated with implied susceptibility to graft-*versus*-tumor reactions may provide a lead for the identification of immunogenic tumor-specific antigens, while all translocations are potential targets for small molecules able to neutralize disease-specific products, such as driver kinases or activation pathways. In patients with deletions or monosomy such efforts might be difficult.

Finally, scores might be influenced by the different treat-

ment possibilities available today. Often large datasets are collected over a long time with considerable changes in first-line therapy, such as introduction of pediatric-based regimens, while the number of patients in different categories remains small. Considering the relative homogeneity of transplant procedures in comparison to the different non-transplant protocols, the post-transplant CIBMTR score represents an important prognostic tool.

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