REFERENCES

Clinical Trials
Comment on Kurosawa et al, page 2113
Self-determinism: alloBMT for AML
Philip L. McCarthy and Theresa Hahn Roswell Park Cancer Institute

In this issue of Blood, Kurosawa et al use a Markov decision process (MDP) of allogeneic hematopoietic cell transplantation (alloHCT) versus chemotherapy in patients with acute myeloid leukemia (AML) in first complete remission (CR1).1

In probability theory, a stochastic or random process is the counterpart to a deterministic process. Instead of dealing with only one possible reality of how the process might evolve over time (eg, solutions of an ordinary differential equation), in a stochastic or random process there is some indeterminacy in its future evolution described by probability distributions.2 To simplify, how can one quantify complicated processes for which there is uncertainty, often at each process step or transition? Andrei Andreyevich Markov, a Russian mathematician, is the father of understanding and quantifying stochastic processes; decision processes that contain elements of uncertainty are often named after him. An online tutorial discusses partially observable MDPs.3

Several investigators have attempted to determine the optimal approach to the clinical management of AML patients in CR1. Strategies have focused on disease characteristics that would predict for a higher risk of relapse such as cytogenetic and molecular markers, ability to attain remission, and other factors including patient age, comorbidities, and donor availability. AlloHCT is associated with a higher early risk of treatment-related mortality (TRM) than chemotherapy and has a unique risk of graft-versus-host disease (GVHD). However, alloHCT is accompanied by the salutary graft-versus-leukemia (GVL) effect that significantly decreases the risk of AML relapse compared with chemotherapy. How can these risks be analyzed along with their effects on quality of life (QOL)? MDP has been implemented for medical decision making when evaluating therapy options along with economic, QOL, and/or outcome analyses.4 However, it has not been used frequently for decision making with regard to the use and timing of alloHCT for hematologic disorders. The first report of MDP for AML patients in CR1 was published in 1996 when the rate of alloHCT-TRM was higher, when only younger patients were eligible for alloHCT and without the benefit of cytogenetic and molecular risk stratification.5 Furthermore, MDPs were conducted for alloHCT in the treatment of chronic myeloid leukemia in the pre- and post-imatinib eras, myelodysplastic syndrome in the pre-demetylation agent era, and also for sickle cell anemia.6-9 The analysis of posttreatment outcomes is complex with competing risks for death such as chemotherapy toxicity, GVHD (alloHCT only), infection, and AML relapse. Thus, statistical models that account for competing risks by multistate modeling or landmark analyses allow clinicians to better determine the risk of various patient outcomes for clinical recommendations.10,11

With a life-threatening disease such as AML, optimizing treatment to prolong survival is the ultimate goal. However, for many patients, in the words of Abraham Lincoln “...it is not the years in your life that count. It is the life in your years.” In the Kurosawa et al analysis, QOL for each state (no relapse without GVHD, no relapse with GVHD, relapse and death for alloHCT in CR1 vs no relapse, relapse, second remission after salvage alloHCT and relapse and death [the lowest QOL measure]) was evaluated by physicians but not by patients. Future analysis might prospectively measure patient-reported QOL outcomes in patients pre- and posttreatment to determine long-term effects of various treatments on QOL that are important to patients. Comparing patient-reported outcomes with physician-assigned QOL—and determining the complexity of interpatient variability in their valuation of QOL and satisfaction with their treatment decision-making—will be very informative. Some individuals place greater value on surviving to experience more of life’s milestones, while others place greater value on the quality of that existence; this applies to physicians, patients, and their caregivers. Understanding decision-making in an era of complex treatment choices will allow physicians and patients to make more informed decisions when faced with the prospect of choosing alloHCT or chemotherapy as the best therapeutic option.

When faced with self-determination (“To do is to be”; Socrates) versus determinism (“To be is to do”; Sartre), preservation of existence (“To be or not to be”; Shakespeare) matters in the context of QOL.

Conflict-of-interest disclosure: The authors declare no competing financial interests.

REFERENCES
Comment on Ensor et al, page 2129

**Childhood ALL: ContRoL it or not?**

André Baruchel  
HOPITAL ROBERT DEBRE AND UNIVERSITY OF PARIS-DIDEROT

In this issue of *Blood*, Ensor et al describe the features associated with the deregulation of CRLF2 signaling in childhood B-cell precursor acute lymphoblastic leukemia. They conclude that CRLF2 deregulation is not an independent predictor of event-free survival.

Cytokine receptor-like factor 2 (CRLF2) or thymic stromal-derived lymphopoietin receptor is a protein encoded by the CRLF2 gene. This gene encodes for a cytokine receptor chain related to γc/IL2Rc. Deregulated expression of CRLF2 results from either a cryptic chromosomal translocation ([t(X;14)(p22;q32)/t(Y;14)(p11.q32)]) or interstitial deletion within the pseudoautosomal region [PAR1]; del(X)(p22.33p22.33)/del(Y)(p11.32p11.32)]. Overexpression of CRLF2 is driven by its juxtaposition to either the IGH@ enhancer (IGH@-CRLF2) or the P2RY8 promoter (P2RY8-CRLF2). This phenomenon has recently been found in B-cell precursor acute lymphoblastic leukemia (BCP-ALL), including Down syndrome patients, lacking recurring chromosomal translocations. CRLF2 deregulation occurs in 5%-7% of childhood ALL but is more frequent among Down syndrome patients (50%-60% of the cases). Overexpression of CRLF2 is associated with activation of the JAK–STAT pathway in cell lines and transduced primary B-cell progenitors, sustaining their proliferation and indicating a causal role of CRLF2 overexpression in lymphoid transformation. Increased CRLF2 expression is in most of the cases associated with a JAK2 mutation, suggesting that mutant JAK2 and CRLF2 may cooperate to contribute to BCP-ALL genesis. To evaluate incidence and clinical and prognostic relevance of CRLF2 deregulation assessed by fluorescence in situ hybridization (FISH) in pediatric ALL, Ensor and colleagues screened 865 BCP-ALL patients treated in the MRC ALL97 trial for the presence of this abnormality and evaluated its effect on outcome within the context of other risk factors. In fact, 2 different UK protocols (ALL 97 and ALL 99) with similar randomized questions (dexamethasone vs prednisone and 6TG vs 6MP) were pooled. Eight hundred sixty-five samples were available from 1725 children included in these 2 consecutive protocols. In a comprehensive multivariate analysis, the CRLF2 deregulation did not remain an independent prognostic factor.

First, the study showed that no matter the criterion (relapse numbers, relapse-free survival [RFS], event-free survival [EFS], or overall survival [OS]) or the population (non-Down syndrome or Down syndrome), the patients with CRLF2 deregulated expression do worse. The impact on OS was significantly in the multivariate analysis. Second, despite the large size of this ALL series, still relatively few patients with CRLF2 rearrangement were analyzed (38 non-Down Syndrome patients and 14 Down syndrome patients). Moreover, these patients were treated in 2 consecutive randomized protocols (ALL97 and ALL99) thus resulting in 8 treatment subgroups. As noted in previous articles from the UK group, the leukemic events were reduced in the dex arms (bone marrow [BM] and [CNS] relapse) and the 6TG arms (CNS relapse). However, in the 6TG arm, deaths in complete remission were more frequent, giving comparable EFS curves for the 2 anti-metabolites. Thus, despite biostatistical adjustments, the low numbers could render the conclusions weaker, especially in the context of these confounding factors.

These results are also to be compared with those published by the BFM study group and the Children’s Oncology Group. In the ALL BFM 2000 study, a high level of CRLF2 expression was found in 9% of the patients (49 of 555 patients) and was associated with a poor EFS. In a multivariate analysis, the presence of P2RY8-CRLF2 (3.8% of the patients) but not a high level of CRLF2 expression—irrespective of the underlying aberration—provided independent prognostic information. This effect was mainly related to a greater cumulative relapse incidence in the so-called non–high-risk patients (classification mainly based on D33 and D78 minimal residual disease evaluation). In the COG P9906 study, CRLF2 rearrangement was documented in 29 of 207 NCI–high-risk patients (14%). This feature was associated with a poor outcome in univariate but not in multivariate analysis, where the deletion of IKZF1 was found to be the sole independent variable associated to the risk of relapse. A deletion of IKZF1 was indeed found in 21 of 29 CRLF2 rearranged cases (72%) and in only 19 of 49 evaluable cases (38%). Those 21 patients with CRLF2 rearrangement and IKZF1 alteration had the worst outcome of the COG-P9906 cohort (estimated RFS at 4 years: 26.4%).

For stratification purposes, it would be useful to know whether non-Down syndrome NCI standard-risk patients (age 1-9, white blood cells < 50 G/L, without initial CNS involvement, without poor-risk cytogenetics) with CRLF2 deregulation do worse than those without in independent cohorts and thus should be excluded from the standard-risk group of non-Down syndrome BCP-ALL.

More globally, many questions have now arisen from the identification of acquired genetic abnormalities in B-lineage ALL, mainly deletion of IKZF1 and deregulation of CRLF2 and JAK2 mutations. Only prospective studies...
Self-determinism: alloBMT for AML

Philip L. McCarthy and Theresa Hahn