of toxicity for some while enhancing the overall likelihood of cure. Now, an increasing understanding of clinically relevant gene mutations and the pathways they impact offers the opportunity to further enhance risk classification and to develop targeted therapies. Bhatia et al now illuminate another critical element in achieving cure: taking your medicine.

Hunger et al recently studied survival among patients with ALL, diagnosed in successive 5-year blocks, and found that survival improved for all subgroups, except infants, from 1990 to 2005. The discrepancy in absolute survival between black and white patients (Asian Americans were not identified as a cohort) decreased from 11% in 1990 to 1994 to 3.3% in 2000 to 2005. This discrepancy is, in part, attributable to a higher incidence of high-risk features among black children and adolescents, but the work of Bhatia et al indicates that significant differences in adherence to oral 6-mercaptopurine (6-MP) may also play a role. Using a medication event monitoring system to measure adherence, they were able to analyze data for 39,803 person-days in 295 patients. Adherence to 6-MP decreased from the end of month 1 to the end of month 5 for the entire cohort, from 95% to 91.8%, but adherence rates among Asian Americans and African Americans were significantly less than those of non-Hispanic whites at 90.0 ± 4.9 and 87.1 ± 4.4%, respectively, compared with 95.2 ± 1.3% (see figure). An adherence rate <90% was associated with a 3.9-fold increase in the risk of relapse, and using this 90% cutoff, 44% of African Americans and 15% of Asian Americans were nonadherent compared with 13% of non-Hispanic whites (P < .0001). Furthermore, 33% of relapses were attributable to nonadherence. Male gender and low maternal education were associated with poor adherence among African Americans, whereas low-income households were linked to poor adherence in Asian Americans. When adherence was assessed in Asian-American and African-American patients from households with higher incomes and maternal education where mothers were full-time caregivers, rates of adherence were comparable to those of non-Hispanic whites.

The findings of Bhatia et al are consistent with those described by the American Academy of Pediatrics Task Force on the Family in 2003. They detail the powerful impact of family well-being on child health and developmental outcomes. Complex living arrangements resulting in loss of stability were linked to poorer health outcomes in children as was chaos in daily living (noise, crowding, and a lack of sustained household routines) and parental psychopathology. Clearly, these factors, compounded by the stressors associated with the diagnosis of cancer in a child, may preclude the establishment of a routine conducive to regimented adherence to oral chemotherapy regimens. Fiese et al, in *Pediatrics*, provided guidelines for pediatricians, urging them to use them to identify the aspects of family structure and function that may impact a child’s health. They also provide a review of educational approaches to promote healthy behaviors that have been of value in noncancer populations. Bhatia et al provide pediatric oncologists with clear guidelines as to the level of adherence that must be achieved to optimize the chance of cure and insight into the factors associated with poor adherence. Like Fiese et al, they are also seeking an approach to support family function and improve adherence. Specifically, this team is currently evaluating the feasibility, utility, and efficacy of an interactive patient education program coupled with a web-based medication scheduling and text-messaging reminder system that uses cell phones to remind parents to give the 6-MP.

Remember that despite the ability to identify subsets of patients with ALL at extremely high risk of relapse based on blast cell genetics and/or measures of response, the majority of deaths in children and adolescents with ALL actually occur among those with good-risk clinical features, because those with a favorable prognosis represent the majority of pediatric patients with ALL. It is conceivable then that many of these better-risk patients have chemotherapy-responsive disease and with adequate adherence will be cured. It may take a village to ensure adequate adherence among all patients with ALL, but the benefit will be significant, and it might be achievable with relatively low-cost interventions.

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REFERENCES


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AML cells maintain a pathological homeostasis between aberrant proliferation and differentiation signals. When chemotherapy is administered, multiple signal pathways are affected. Apoptosis and, as a result, desired clinical response are induced in cases where the above-mentioned balance is impaired in either direction (upper panels). In cases illustrated in the lower panel, both signals are derived from powerful genetic aberrations and balance is maintained despite chemotherapy-induced stress resulting in the survival of the leukemic cells.

(SWOG) studies. Focusing on patients presenting with a normal karyotype and FLT3/ITD, the authors provide convincing evidence that conventional induction is much less effective in patients expressing both NUP98/NSD1 and FLT3/ITD than in any other patient subpopulation. In their mostly pediatric cohort, the overall prevalence of NUP98/NSD1 was 3% (45/1421), but it was as high as 15% in patients presenting with FLT3/ITD. It is therefore worth questioning whether screening for NUP98/NSD1 fusion transcript in AML patients presenting with a normal karyotype and FLT3/ITD should be mandatory, particularly in pediatric population.

Recent progress in gene sequencing allows rapid coverage of a wide spectrum of genes at an affordable cost. In the very near future, comprehensive genetic data could become available at least for most AML patients diagnosed in developed countries. However, the capacity to identify all genetic aberrations at the DNA level, describe and quantify gene expression at the RNA level, and even analyze epigenetic profile, has not been widely adopted by clinicians. Unfortunately, the availability of such an enormous volume of data has not yet changed treatment algorithms for most AML patients. Several groups collected genetic data from a large number of AML patients, mostly those treated according to a uniform protocol, differentiated them based on their prognosis into genetically distinguishable groups and created a generic prediction model. Due to statistical constraints, in most models, the number of analyzed genetic parameters is limited to those that are most prevalent or considered to have the strongest clinical influence, and thus, most of available genetic data are excluded. Although several such models have been reported, none of them includes rare genetic aberrations such as NUP98/NSD1. Most models yield comprehensive risk stratification, yet they are mainly designed to support patient selection for allogeneic hematopoietic stem cell transplantation and neglect a preferred induction approach.

Ostronoff et al report that, within the group of patients diagnosed with normal karyotype AML, those presenting with both FLT3/ITD and NUP98/NSD1, FLT3/ITD alone, and NUP98/NSD1 alone achieved a complete remission rate of 37%, 67%, and 86%, respectively. Although based on data of only 11 patients, in cases where WT1 mutation was identified in addition to the former 2 aberrations, the complete response rate dropped to as low as 9%. Such a significant bedside finding should be taken back to the bench with an aim to explore mechanisms of interaction between these genes that antagonize chemotherapy effect. Understanding the biological mechanism underlying this exceptional synergistic effect is of particular interest because these 2 aberrations are not known to act within the same signaling pathway.

Twelve years ago, Gilliland and Griffin suggested that the FLT3/ITD mutation, whereas providing a strong proliferative signal, is not sufficient for leukemia initiation. According to this well-appreciated concept, mutations of 2 different classes, one that enhances proliferation and the other that impairs differentiation, are required for leukemia initiation. The model by Gilliland and Griffin highlights a fundamental take-home message in the biology of leukemia, ie, the significance of interaction between different genes. FLT3/ITD may coexist with many other mutations but only few specific gene pairs including the FLT3/ITD and NUP98/NSD1 combination are powerful enough to initiate leukemia.

If, as suggested by Gilliland and Griffin, in all AML cells an aberrant proliferative signal is present along with impairment in differentiation process, it is interesting to decipher what makes cells harboring the FLT3/ITD and NUP98/NSD1 combination so resistant to chemotherapy. FLT3/ITD, is a strong driver for proliferation and beyond conventional cytogenetics, is the most common genetic aberration of definitive clinical significance in AML. The second player in this scene, NUP98/NSD1, is a fusion between a regulator of protein and RNA nucleo–cytoplasmic transport (NUP98) and histone methyltransferase (NSD1). In various hematological malignancies, 30 different genes including NSD1 have been identified to partner NUP98 for the creation of an oncogenic fusion transcript. NUP98 aberrant transcripts were shown to significantly impair differentiation, resulting in a variable biological effect correlating with the specific NUP98 partners. Patient specific prognosis is therefore determined by the level of biological interaction between fusion partners on the one side and the collaborative proliferation signal on the other.

Ostronoff et al also screened 80 acute promyelocytic leukemia (APL) patients: 30 (37.5%) were FLT3/ITD positive but none expressed NUP98/NSD1. Given that the presence of FLT3/ITD does not hamper
prognosis of APL patients treated with therapy aimed to overcome differentiation blockade, the strength of the second hit seems to be a major component that differentiates APL from other types of AML. Following this line of thought, it may be suggested that in AML cells, apoptosis is induced by therapy, if chemotherapy significantly alters the inner cell balance between proliferation and differentiation signals (see figure).

Coexpression of 2 powerful drivers such as FLT3-ITD and NUP98/NSD1 creates a stable pathological balance that drives leukemia forward but is very difficult to disrupt by regular chemotherapies.

One conclusion from the study by Ostronoff et al is that AML patients coexpressing FLT3-ITD and NUP98/NSD1 may require alternative therapies. In vitro data suggest that FLT3 inhibitors may be an option. Unfortunately, no clinical evidence favoring specific agents exist for patients presenting with both FLT3-ITD and NUP98/NSD1. In addition, because NUP98 may partner multiple other genes yielding oncogenic signals, it is worth exploring the clinical effect of other NUP98-related fusion transcripts. It might also be suggested that characterization of the interaction between proliferation and differentiation signals as a whole (may be by RNA expression patterns) may help progressing toward personalizing clinical decisions in AML. Leukemia patients presenting with a combination of a strong proliferation driver mutation and a dominant differentiation blocker are likely to require novel specific therapies.

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Concealed dagger in FLT3/ITD⁺ AML

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