Cure of childhood ALL: exacting a lower toll

The unpredictable oncogenic effects of contemporary treatment for childhood acute lymphoblastic leukemia (ALL) warrant continuous long-term monitoring of patients for second neoplasms. Bhatia and colleagues (page 4257) in the Children’s Cancer Group (CCG) reported cumulative rates of second neoplasms of 1.18% (95% CI, 0.8% to 1.5%) at 10 years and 2.08% (95% CI, 1.4% to 2.8%) at 15 years among 8831 patients treated for childhood ALL between 1983 and 1995. Not surprisingly, irradiation and a history of relapse were associated with an increased risk for the development of a second cancer. The excess risk in females largely reflected an increased incidence of soft tissue sarcomas, for reasons that remain obscure.

The findings agree with those reported by several other groups: 3.3% at 15 years in clinical trials of the Berlin-Frankfurt-Münster group, 2.7% at 18 years in those of the Dana-Farber Cancer Institute, and 2.9% at 20 years in the studies conducted in the Nordic countries. But the median follow-up times of these studies ranged from 4.6 years to 7.6 years, and none had adequate observations beyond 20 years. While the cumulative incidence of therapy-related acute myeloid leukemia in the CCG study reached a plateau within 11 years, there was a continuous rise in the rates of brain tumors and other solid tumors (irradiation-related second neoplasms; see Bhatia et al’s Figure 1). Thus, one would predict additional cases of second neoplasms with extended monitoring. Indeed, my colleagues and I have observed a steady rise in the cumulative incidence of second neoplasms, to above 20% at 30 years, in a cohort of patients who received radiation (C.-H. P. et al, unpublished data). Fortunately, most of the second neoplasms of very late onset were benign or were low-grade malignancies (eg, basal cell carcinoma and meningioma) with a median latency period of 27 and 22 years, respectively. These results underscore the importance of greatly extended follow-up in fully appreciating the oncogenicity of leukemia treatment programs.

Bhatia and colleagues found no difference in the incidence of second malignancies within the first 5 years of follow-up between patients treated in the early (1983 to 1989) and recent (1989 to 1995) eras. It is reassuring that more intensive use of chemotherapy in contemporary trials did not increase the risk of development of acute myeloid leukemia, which has a relatively short incubation period. Given the fact that irradiation was administered to 51% of patients in the early era, compared with only 28% in the recent era, the final cumulative incidence of second neoplasms in the latter cohort will likely be lower than in the former. With the trend toward reduced use of cranial irradiation at lower doses (eg, 12 Gy), we anticipate a significant decrease in the incidence of second neoplasms in patients entered in ongoing clinical trials.

Recent studies show that the genetic polymorphisms of many drug-metabolizing enzymes are associated with the development of second cancers. We and others have demonstrated that individuals with a deficiency of thiopurine methyltransferase, an enzyme that catalyzes the inactivation of thiopurines, are at increased risk of developing therapy-related leukemia, especially when they received concomitant epipodophyllotoxin therapy, and irradiation-related brain tumors when intensive antimetabolite therapy is given before and during cranial irradiation. Apparently, antimetabolites can potentiate the carcinogenic effects of epipodophyllotoxins and irradiation. Polymorphisms of glutathione S-transferase (GSTP1), NAD(P)H:quinone oxidoreductase, and cytochrome P450 3A4 have also been linked to an increased risk of therapy-related leukemia, because of the decreased inactivation of carcinogens or mutagens or increased production of reactive metabolites. Remarkably, by using DNA microarray analysis, my colleagues and I recently found that a certain gene expression profile at diagnosis of ALL predicts the development of therapy-related leukemia (Yeoh et al, Cancer Cell. 2002;1:133-143). These results suggest that similar studies might identify individuals who are at greatest risk for any therapy-related cancer, thus pointing the way to optimal therapy.

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