To the editor:

On the malignant potential of thiopurine therapy

With great interest we have read the paper by Schmiegelow and colleagues describing the increased risk of developing a second malignant neoplasm, especially acute myeloid leukemia and myelodysplastic syndromes, due to maintenance therapy with 6-mercaptopurine (6-MP) and methotrexate after childhood acute lymphoblastic leukemia. An impaired thiopurine S-methyltransferase (TPMT) activity, high 6-thioguaninenucleotides (6-TGN) and elevated 6-methylmercaptopurine-ribonucleosides (6-MMPR) levels were found to be risk factors. An increasing number of relatively young patients with different autoimmune diseases (eg, inflammatory bowel disease) or after organ transplantations are treated with a life-long thiopurine regime. The exact role of thiopurines in developing hematologic malignancies is unknown, but it has been postulated that the inactivation of the DNA mismatch repair system may lead to an increased rate of spontaneous mutations.

Here we propose an additional theory from a more pharmacodynamic point of view. An intrinsic complication of thiopurine therapy is that this cytotoxic and apoptosis-inducing agent can target almost all human cells, particularly myeloid precursor cells, and may induce genetic alterations. Children with acute lymphocytic leukemia treated with chemotherapy, including 6-MP, developed a high number of mutations at the hypoxanthine-guanine phosphoribosyltransferase (HGPRT)–reporter gene. In addition, azathioprine therapy in insulin-dependent diabetes mellitus patients resulted in an increase of HGPRT T cell–mutant frequencies that was statistically correlated with duration of therapy. All clinically used thiopurines have to be metabolized by the enzyme HGPRT to become pharmacologically active. Impaired HGPRT activity due to mutations may therefore lead to a relative failure of therapy. More importantly, mutated cells are thereby thiopurine refractory and thus positively selected and amplified, as all other cells will become apoptotic due to therapy. This process of selection of mutated cells due to thiopurine administration may give rise to an increased risk of developing hematologic malignancies such as leukemia or myelodysplastic syndromes. The risk factors diminished TPMT activity, high 6-TGN, and 6-MMPR levels that were observed by Schmiegelow and colleagues fit in with this theory. All these pharmacodynamic aspects indicate at an increased rate of elimination of nonmutated cells due to high levels of the pharmacologically active thiopurine metabolites, which eventually leads to an accelerated selection of HGPRT-mutated cells. These patients are probably at risk to develop a hematologic malignancy earlier than patients with a more common and more prevalent type of thiopurine metabolism, that is, those patients using usual, average TPMT activity. Studies are warranted to further explore the field of genotoxicity and mutagenicity of thiopurine therapy, as more and more patients are being treated with a lifelong regime.

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References

Response

Could mutations in the hypoxanthine-guanine phosphoribosyl transferase gene induced by thiopurine therapy promote the development of second malignant neoplasms?

The primary cytotoxic metabolite of 6-mercaptopurine (6MP) and other thiopurines are the 6-thioguanine nucleotides (6TGN), which are incorporated into DNA. Thus, during 6MP/methotrexate (MTX) therapy, 1 in 10^3 to 10^4 DNA nucleotides of circulating cells are substituted 6TGN, which may interfere with postreplicative DNA mismatch repair and induce therapy-related malignant clones. Such clones may arise very early in therapy, that is, months or years before the therapy-related cancer becomes clinically overt. It is still unknown how thiopurine therapy influences the proliferation and expansion of such clones. de Boer and colleagues propose that thiopurine-induced mutations in the hypoxanthine-guanine phosphoribosyl transferase (HGPRT) gene could render these clones resistant to further 6MP therapy and thus offer them a proliferative advantage compared with their normal counterparts. Although all second cancers occurred after cessation of therapy in the Nordic Society of Paediatric Hematology and Oncology acute lymphoblastic leukemia (ALL) 92 study, the median time to diagnosis of 16 cases of therapy-related acute myeloid leukemia and myelodysplastic syndromes (t-AML/MDS) was only 3.7 years from the diagnosis of ALL. Two lines of research could clarify the natural history of thiopurine-induced t-AML/MDS. First, by identifying the exact chromosomal breakpoints of the t-AML/MDS and...
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