

Review Article

Assessment of Thiopurine-based drugs according to Thiopurine S-methyltransferase genotype in patients with Acute Lymphoblastic Leukemia

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Abstract

For the past half century, thiopurines have earned themselves a reputation as effective anti-cancer and immunosuppressive drugs.

Thiopurine S-methyltransferase (TPMT) is involved in the metabolism of all thiopurines and is one of the main enzymes that inactivates mercaptopurine. 6-MP is now used as a combination therapies for maintenance therapy of children with acute lymphocytic leukemia (ALL). In all patients receiving mercaptopurine, there is a risk of bone marrow suppression.

TPMT activity is inherited as a monogenic, co-dominant trait. More than 25 variants are known. Genetic testing is available for several TPMT variant alleles. Most commonly TPMT*2, *3A, and *3C are tested for, which account for >90% of inactivating alleles. Differences in DNA that alter the expression or function of proteins that are targeted by drugs can

contribute significantly to variation in the responses of individuals. Genotyping may become part of routine investigations to help clinicians tailor drug treatment effectively. This success is mainly due to the development of combination therapies and stratification of patients according to risk of treatment failure and relapse, rather than the discovery of new drugs. The aim of this study was to investigate the effect of genotype or methyltransferase enzyme activity before starting therapy in children with ALL. This can prevent the side effect of thiopurine drugs. In fact, the common polymorphism of this enzyme in population could be a prognostic factor in relation to drug use and treatment of patients with ALL.

Keywords

Acute lymphoblastic leukemia; Azathioprine; 6-Mercaptopurine; 6-Thioguanine; Myelosuppression; Polymorphism

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Introduction

Since the introduction of combination chemotherapy for the treatment of acute lymphoblastic leukemia (ALL) in children, the prognosis for this disease has improved steadily such that most trials now report a long-term survival rate of over 70%. However, current treatment protocols are complex and are associated with significant toxicity [1].

There are therefore two major priorities in the treatment of childhood ALL; further improvement in the survival rate and a reduction in treatment-associated toxic side effects. One method, which may be used to achieve these goals, is the more effective

use of currently available chemotherapy. At present, most patients are given cytotoxic drugs at a dosage determined by their surface area, despite the fact that, for several of the agents used, there is good evidence that this results in marked differences in the amount of drug which reaches its target [2]. This is exemplified by the thiopurine, 6-mercaptopurine (6-MP), used in many regimes as part of the maintenance phase of therapy.

The level of expression of the enzyme thiopurine methyltransferase (TPMT) is an important determinant of the metabolism of thiopurines used in