|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | No variant in *TPMT* | | | Heterozygous variant in *TPMT* treated  with the standard dose | | | Heterozygous variant in *TPMT* treated  with 50% of the standard dose | | |
| Adverse event | Total (%) | AZA (%) | MP (%) | Total (%) | AZA (%) | MP (%) | Total (%) | AZA (%) | MP (%) |
| Hepatotoxicity | 110 (16) | 51 (11) | 59 (24) | 3 (9) | 1 (5) | 2 (17) | 3 (8) | 3 (13) | 0 |
| Leukopenia | 49 (7) | 19 (4) | 30 (12) | 8 (24) | 4 (18) | 4 (33) | 1 (3) | 1 (4) | 0 |
| Gastrointestinal side effects | 317 (46) | 197 (44) | 120 (49) | 16 (47) | 11 (50) | 5 (42) | 12 (32) | 8 (33) | 4 (29) |
| Total | 695 | 448 | 247 | 34 | 22 | 12 | 38 | 24 | 14 |

**Supplementary Table 2.** Side effect rates in patients without a genetic variant in *TPMT* and those with a heterozygous variant in *TPMT* treated with either the full dose or reduced thiopurine dose.

See the Method section for definitions of hepatotoxicity, leukopenia and gastrointestinal side effects. In the TOPIC trial patients were randomized for thiopurine dosing based on their *TPMT* genotype versus the standard dose. Only patients assigned to the *TPMT* genotyping arm received a 50% dose reduction when they carried a heterozygote variant in *TPMT*. This resulted in the formation of three subgroups. First, there is the largest group of patients without a variant in *TPMT* (randomized to either the intervention group or standard group) treated with the full dose thiopurine. Second, a small group was randomized to the invention arm and received 50% of the regular dose because of the presence of a variant in *TPMT*. The third group is also a small group randomized to the ‘standard of care arm’ and therefore received the full regular dose, while genotyping after the conduction of the clinical trial revealed that these patients carried a heterozygote variant in *TPMT*. Chi-squared tests were conducted to compare rates between patients in the three groups. These analyses showed that there was a significant difference in leukopenia rate between the three groups (p=0.001), but not for gastrointestinal side effects (p=0.23) or hepatotoxicity (p=0.24). Absolute numbers are very low, which results in insufficient power to perform additional statistics to compare AZA with MP within the small subgroups. Taking the small groups into account no large differences were seen in frequencies between AZA and MP for the subgroups.

AZA, azathioprine; MP, mercaptopurine; TPMT, thiopurine S-methyltransferase.