Screening patients for fluoropyrimidine-related toxicity risk: The most effective method to save lives


BACKGROUND:
Severe, sometimes fatal, toxicity can occur during the 1st or 2nd course of chemotherapy using fluoropyrimidines (FPs), and poses a serious public health problem. FPs carry a 3-5% risk of grade 3 early toxicities and 0.2% risk of death, linked to Dihydropyrimidine Dehydrogenase (DPD) deficiency. Methods: Of the 23,000 patients screened before chemotherapy since July 2000 in our laboratory, 472 were referred to us due to severe toxicity during the 1st round of FPs, or because pre-screening was done too late. Toxicity scale analysis performed according to the NCI scale of adverse reactions to cancer drugs (0=none, 5=death). Patients were previously FPs naïve, had different cancers, and received various protocols (FEC, LV5FU2, FOLFOX, FOLFIRI). Capable/tat, LFT with or without EGFR or VEGF monoclonal antibodies). The reliability of the following 4 pre-treatment screening tests to predict grade ≥ 4 toxicity was assessed:
1) DPDY genotype mutations (2A, 9B, 13, HapB3)
2) Plasma uracil (U) level
3) Metabolic Index: dihydropyrimidine/uracil ratio (UH7/2)
4) Multiparametric approach integrating genotyping, U and uracil quantification, UH7/2 ratio and key patient factors (age, sex, etc.). Statistics: Sensitivity or probability of detection, measures the proportion of true positives for DPD deficiency that are correctly identified as such. False negative: A false negative is a test result that indicates a person does not have DPD deficiency when the person actually does have it. McNemar’s test with Bonferroni correction was used for statistical analysis.

RESULTS: Of the 472 referred patients, 169 had grade ≥ 4 toxicity, or of whom, 41 died from toxicity.

1) DPDY genotype mutations:
- Overall, 96 patients had one or more DPDY mutations: 37 (37.7%) 2A; 42 (42.6%) 9B; 3 (3%) 13; 8 (8.1%) HapB3; 3 were homozygous 2A, 1 was heterozygous 2A 9B, 1 was heterozygous 2A 13.
- Grade 4 and 5 toxicities were found in the following percentages of patients with each of the mutations identified: 68% for 2A, 71% for 9B, 100% for 13; 38% and for 38% for HapB3.

2) Plasma Uracil (U) level:
- 21.8% of patients with plasma uracil concentration ≥ 16 ng/ml presented with grade 4-5 toxicities and 2.9% died as a result.
- In the intermediate group (16ng/ml-U<150ng/ml), 52.8% presented with grade 4-5 toxicities of whom 11.8% died. 28% presented with grade 3 toxicity. Thus we can conclude that 19.2% of these patients did not present with toxicity and therefore were potentially under-dosed.
- All of the patients with a plasma uracil level ≥ 150 ng/ml presented with ≥ Grade 4 toxicity. NB: 14.7% of patients with plasma uracil levels of < 150 ng/ml had grade 5 toxicity.

3) Metabolic Index (UH7/2):
- 13.5% of patients with a ratio of ≥ 6 presented with grade 4-5 toxicities and 1.5% died.
- With ratios of 2-5 UH7/2, 60% of patients experienced grade 4-5 toxicities and 36.7% had grade 3. That leaves 3.3% who did not present with toxicities and who were potentially under-dosed, which would have been detrimental to the success of their treatment.
- 100% of patients with a ratio of ≥ 2 presented with ≥ Grade 4 toxicity. NB: 12.6% of patients with a ratio of 2 had grade 5 toxicity.

4) Multiparametric approach:
- 3.9% of patients who were evaluated as being not DPD deficient (versus 21.8% and 13.5% for plasma uracil levels and UH7/2 respectively) presented grade 4-5 toxicities and 0.5% died (versus 2.9% and 1.5% for plasma uracil levels and UH7/2 ratio respectively. Adding in the grade 3 toxicities. 5.8% incorrectly identified as being not DPD deficient experienced ≥ Grade 3 toxicities. This is significantly inferior to the results obtained with the plasma uracil level and UH7/2 ratio methods, 38.6% at 25.1% respectively.
- In the group of partially DPD-deficient patients, 56.9% will present with grade 4-5 toxicity and 38.9% with Grade 3. This means that 4.2% of patients did not experience toxicity and were potentially under-dosed, which is significantly inferior to the 19% under-dosed by the plasma uracil level method.
- 100% of the patients evaluated as completely DPD deficient presented ≥ Grade 4 toxicities.

CONCLUSION: The most effective screening method

When the multiparametric approach is statistically (p<0.001) the most efficient in terms of preventing grade 4 and 5 toxicity (death) following treatment with FPs. Around 290,000 patients are treated with FPs per year in the USA. Assuming a 0.2% mortality rate due to toxicity, around 580 lives could be saved per year by using the multiparametric pre-treatment test.