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

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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.

METHOD:

Of 29,000 patients screened since July 2000, 472 were referred to us due to severe toxicity during 1st round 5-FU, or because pre-screening was done too late. Toxicity evaluation was performed according to the NCI scale of adverse reactions to cancer drugs (0=none, 5=death). Patients were previously 5-FU naïve, had different cancers, and received various protocols, eg. 5FU *or* Capecitabine; bolus±continuous *or* per os.

The reliability of the following 4 pre-treatment screening tests to predict grade≥ 4 toxicity was assessed: 1) DPYD genotype mutation (*2A,*2B,*7, 13, HapB3) 2) Plasma uracil (U) level, 3) Plasma dihydrouracil/uracil ratio (UH_2/U) 4) a multiparametric approach with genotyping, UH_2/U ratio and key patient factors (age, sex, etc.).

McNemar's test with Bonferroni correction was used for statistical analysis.

RESULTS:

Of the 472 referred patients, 169 had grade 4 or 5 toxicity, of which 41 died from toxicity. 98 had one or plus *DPYD* mutation: 42(42.9%)*2A; 43(43.9%)*2B; 3(3%)*7; 4(4%)*13; 8(8.16%) HapB3; 1 was homozygous *2A.

Data below compare the 4 screening methods for predicting grade 4-5 toxicity:

Grade 4-5 tox	***DPYD* Mutations**	**Uracil >16ng/ml**	**UH_2/U <6**	**Multiparametric**
n	169	169	169	169
Sensitivity n (%)	68 (40,23%)	108 (63,9%)	133 (78,69%)	161 (95,27%)
False negative n (%)	101 (59,76%)	61 (36,1%)	36 (21,3%)	8 (4,73%)

Grade 5 tox	***DPYD* Mutations**	**Uracil >16ng/ml**	**UH_2/U <6**	**Multiparametric**
n	41	41	41	41
Sensitivity n (%)	20 (48,78%)	33 (80,5%)	37 (90,24%)	40 (97,56%)
False negative n (%)	21 (51,22%)	8 (19,5%)	4 (9,76%)	1 (2,44%)

CONCLUSION :

The multiparametric approach is statistically ($p<0.0001$) the most efficient in terms of preventing grade 4 and 5 toxicity (death) due to 5-FU treatment. Around 290,000 patients are treated with 5-FU per year in the USA. Assuming a 0.2% mortality rate due to toxicity, around 580 lives could be saved per year using the multiparametric pre-treatment test.