

Germline polymorphisms in patients with advanced nonsmall cell lung cancer receiving first-line platinum-gemcitabine chemotherapy: a prospective clinical study

Markus Joerger, Sjaak A Burgers, Paul Baas, Egbert F Smit, Tjeerd J Haitjema, Martin P L Bard, Valerie D Doodeman, Paul H M Smits, Andrew Vincent, Alwin D R Huitema, Jos H Beijnen & Jan H M Schellens

BACKGROUND

The authors assessed the impact of germline polymorphisms on clinical outcome in patients with advanced nonsmall cell lung cancer (NSCLC) who received platinum-gemcitabine (PG) chemotherapy.

METHODS

In total, 137 patients with stage IIIB/IV NSCLC were included who received first-line PG chemotherapy (74% of patients received cisplatin, and 26% received carboplatin). Twenty-three germline polymorphisms that were identified in peripheral blood samples were analyzed for progression-free survival (PFS), treatment response, overall survival (OS), and toxicity.

RESULTS

The median PFS was 5.8 months, the median OS was 10.2 months, and 44 patients (32%) had a partial treatment response. Carriers of the excision repair cross-complementation group 1 (ERCC1) mutant thymine (T) allele had a lower treatment response rate (29% vs 52%; $P = .02$), shorter PFS (adjusted hazard ratio [HR], 1.60; $P = .04$), and shorter OS (adjusted HR, 1.54; $P = .05$) compared with carriers of the wild-type cytosine/cytosine (CC) genotype. The xeroderma pigmentosum group A member 10 (XPB10) mutant adenine (A) allele (adjusted HR, 0.64; $P = .04$) and the x-ray cross-complementing group 1 (XRCC1) mutant guanine (G) allele (adjusted HR, 0.51; $P = .02$) also were independent predictors of OS. Carriers of the mutant adenosine triphosphate-dependent DNA helicase Q1 (RECQ1) C allele or the mutant cytidine deaminase (CDA) C allele were more likely to experience severe leukocytopenia (26% vs 10% [$P = .03$] and 28% vs 11% [$P = .02$], respectively) compared with wild-type genotype carriers. Patients who carried the homozygous mutant glutathione S-transferase π 1 (GSTP1) GG genotype were at considerable risk for severe platinum-associated polyneuropathy (18% vs 3% in wild-type vs heterozygous mutant patients, respectively; $P = .01$).



CONCLUSIONS

To the authors' knowledge, this is the first prospective study to date in patients with advanced NSCLC describing predictive germline polymorphisms not only for the clinical activity of PG chemotherapy (ERCC1, XPD10) but also for its toxicity (GSTP1, RECQ1, CDA). Nonplatinum-containing chemotherapy in carriers of the ERCC1 T allele or the XPD10 G allele should be studied prospectively.

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