Open-label, randomized study of individualized, pharmacokinetically (PK)-guided dosing of paclitaxel combined with carboplatin or cisplatin in patients with advanced non-small-cell lung cancer (NSCLC)


BACKGROUND
Variable chemotherapy exposure may cause toxicity or lack of efficacy. This study was initiated to validate pharmacokinetically (PK)-guided paclitaxel dosing in patients with advanced non-small-cell lung cancer (NSCLC) to avoid supra- or subtherapeutic exposure.

PATIENTS AND METHODS
Patients with newly diagnosed, advanced NSCLC were randomly assigned to receive up to 6 cycles of 3-weekly carboplatin AUC 6 or cisplatin 80 mg/m(2) either with standard paclitaxel at 200 mg/m(2) (arm A) or PK-guided dosing of paclitaxel (arm B). In arm B, initial paclitaxel dose was adjusted to body surface area, age, sex, and subsequent doses were guided by neutropenia and previous-cycle paclitaxel exposure [time above a plasma concentration of 0.05 µM (Tc>0.05)] determined from a single blood sample on day 2. The primary end point was grade 4 neutropenia; secondary end points included neuropathy, radiological response, progression-free survival (PFS) and overall survival (OS).

RESULTS
Among 365 patients randomly assigned, grade 4 neutropenia was similar in both arms (19% versus 16%; P = 0.10). Neuropathy grade ≥2 (38% versus 23%, P < 0.001) and grade ≥3 (9% versus 2%, P < 0.001) was significantly lower in arm B, independent of the platinum drug used. The median final paclitaxel dose was significantly lower in arm B (199 versus 150 mg/m(2), P < 0.001). Response rate was similar in arms A and B (31% versus 27%, P = 0.405), as was adjusted median PFS [5.5 versus 4.9 months, hazard ratio (HR) 1.16, 95% confidence interval (CI) 0.91-1.49, P = 0.228] and OS (10.1 versus 9.5 months, HR 1.05, 95% CI 0.81-1.37, P = 0.682).
CONCLUSION
PK-guided dosing of paclitaxel does not improve severe neutropenia, but reduces paclitaxel-associated neuropathy and thereby improves the benefit-risk profile in patients with advanced NSCLC.

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