Gemcitabine and pemetrexed combination: the key role of the sequence of drugs administration

We read with interest the report by West et al. [1] who evaluated the activity of gemcitabine–pemetrexed combination.
in patients with advanced non-small-cell lung cancer (NSCLC). In this trial, gemcitabine was given on days 1 and 8 and pemetrexed immediately following day 8 gemcitabine.

The authors found an overall response rate of 13%, with a similarly disappointing progression-free survival. They concluded that these results, combined with a challenging hematologic toxicity, limit the appeal of this combination.

In spite of this conclusion, preclinical and clinical data indicate a schedule-dependent synergism between pemetrexed and gemcitabine and support the hypothesis that the negative results reported in this trial could depend on the sequence of drugs administered.

Pemetrexed acts on several pathways, involved in DNA synthesis and cell death control; in particular, deoxycytidine triphosphate depletion and glycaminide ribonucleotide formyltransferase inhibition by pemetrexed might enhance the expression of the key genes involved in gemcitabine transport and metabolism, as reported in several preclinical cancer models, including NSCLC cells. Consistent with this observation, several in vitro experiments showed that the sequence pemetrexed → gemcitabine is more active than gemcitabine → pemetrexed [2, 3] and their synergistic interaction was associated with the induction of the gemcitabine critical genes deoxycytidine kinase and human equilibrative nucleoside transporter-1 expression by pemetrexed [4, 5]. Moreover, these preclinical data are consistent with the results of a randomized phase II trial testing three different schedules of pemetrexed and gemcitabine in combination [6]. In this study, patients were randomly assigned to three schedules of pemetrexed plus gemcitabine, separated by a 90-min interval: pemetrexed followed by gemcitabine on day 1 and gemcitabine on day 8; gemcitabine followed by pemetrexed on day 1 and gemcitabine on day 8; and gemcitabine on day 1 and pemetrexed followed by gemcitabine on day 8. The schedule pemetrexed → gemcitabine was less toxic compared with the other sequences and was the only schedule that met the protocol-defined efficacy criteria, obtaining a confirmed response rate of 31%.

Although the discrepancy between the low activity and high toxicity observed by West et al. is difficult to interpret, it could be due to pharmacogenetic changes induced by the two drugs, and depending on the order in which they are administered may also underlie the different toxic effects observed.

The evidence of a synergistic interaction between pemetrexed and gemcitabine and the available clinical evidence of antitumor activity of their combination in treating patients with NSCLC support further investigation to optimize the toxicity and efficacy of this regimen.

The negative results obtained in the trial by West et al. [1], consistent with already available preclinical and clinical data, support the use of the sequence pemetrexed → gemcitabine.

**References**


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