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GYNAECOLOGICAL CANCER

Vintafolide—targeting the folate receptor with a cytotoxic offers hope

Phase II data from the PRECEDENT trial has shown that women with platinum-resistant ovarian cancer might gain some benefit with vintafolide, a new drug conjugate comprising desacetylvinblastine and folic acid. For these patients, who invariably have poor prognoses, this comes as welcome news.

“Platinum-resistant ovarian cancer is difficult to treat and, prior to this study, about a dozen randomized trials had been conducted in this patient population,” explains lead investigator Wendel Naumann. “All of these trials were negative, with the exception of the recent AURELIA trial. Similar to AURELIA, our study demonstrated an improvement in progression-free survival. Unfortunately, PRECEDENT was underpowered to show a survival advantage.”

More than 80% of epithelial ovarian cancers express the folate receptor, a vitamin transporter not typically expressed by healthy cells. Accordingly, its differential expression profile makes the folate receptor an attractive target for therapy. Furthermore, patients whose tumours highly express the folate receptor have poorer prognoses than those whose tumours are receptor-negative. Vintafolide was designed to bind the receptor selectively via its folate domain and deliver the cytotoxic agent (the vinblastine derivative) in a targeted manner straight to tumour cells, sparing healthy cells.

Patients who had undergone up to two previous regimens of chemotherapy were enrolled in the PRECEDENT study, either receiving the standard of care of pegylated liposomal doxorubicin (PLD) with or without vintafolide. In the intention to treat population ($n = 149$), the median progression-free survival (PFS) was 5.0 months for the combination therapy and 2.7 months for PLD alone. Common adverse effects of treatment included leukopenia and peripheral sensory neuropathy. In total,

eight patients (7.5%) abandoned treatment due to treatment-related adverse effects.

One of the benefits of this strategy is that as well as being selectively cytotoxic, an accompanying agent— ^{99m}Tc -etarfolide—has been developed to assess the extent of folate receptor expression. “This companion diagnostic test predicts if patients are able to respond to this treatment or not,” explains Naumann. The imaging agent selectively binds the folate receptors and can be visualized with single-photon emission CT (SPECT).

Indeed, in patients whose lesions all expressed the folate receptor, the response to vintafolide and PLD combination therapy was most pronounced: median PFS was 5.5 months compared with only 1.5 months for those receiving PLD alone. “Seeing a PFS with a hazard ratio benefit of 0.38 is truly remarkable and very encouraging, especially with a drug that has limited toxicity,” says Naumann. Furthermore, in those patients with some degree of folate-receptor expression (10–90%), vintafolide also imparted some PFS benefit, whereas those without folate receptor expression did not benefit (HR 0.87 and HR 1.81, respectively).

Naumann is optimistic about the future of vintafolide in the clinic: “I think vintafolide will likely be the first cytotoxic chemotherapy that will be approved in almost 10 years—gemcitabine was the last—and likely to become part of the standard of care in women with platinum-resistant ovarian cancer.” Indeed, a phase III trial—PROCEED—is currently enrolling patients in the USA and Europe (NCT01170650).

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Original article Naumann, W. J. *et al.* PRECEDENT: a randomized phase II trial comparing vintafolide (EC145) and pegylated liposomal doxorubicin (PLD) in combination versus PLD alone in patients with platinum-resistant ovarian cancer. *J. Clin. Oncol.* doi:10.1200/JCO.2013.49.7685