EUROPEAN JOURNAL OF CANCER 45 (2009) 1330–1332

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Editorial

Positioning pemetrexed in the treatment of ovarian cancer

Progress in overcoming drug resistance in ovarian cancer has been slow over the last decade. There is a need to develop mechanisms to avoid or prevent resistance, or to develop new drugs to target key cellular process to improve the survival of the fourth most common cause of death from malignant disease in women. For most women, advanced ovarian cancer remains incurable but a small subgroup of patients are cured by a combination of surgery and chemotherapy, raising hopes that novel therapeutic agents might further increase survival. Thus far attempts to improve on the platinum-paclitaxel doublet with a third drug have also proved disappointing, and efforts have been made to increase the number of compounds available to treat subsequent relapses.

Anti-folate drugs were among the first anti-cancer agents. Dramatic responses were seen initially in leukaemias and methotrexate, a synthetic and less toxic analogue of aminopterin was introduced into the clinic 60 years ago and heralded the future of medical oncology. The principal mode of action of methotrexate is through inhibition of dihydrofolate reductase (DHFR) and the drug is active in many solid tumours, and is generally well tolerated. There followed a generation of scientific endeavour to improve our understanding of folate pathways in cancer with the hope of finding more effective drugs. Consequently, a large number of newer and more potent anti-folate drugs have been developed.[1] Pemetrexed, the latest one to reach the 'market', is a multi-target anti-folate, inhibiting binding of natural folates required for key enzymes such as thymidylate synthase (TS), DHFR, glycinamide ribonucleotide formyl transferase (GARFT) and aminoimadazole carboxamide ribonucleotide formyl transferase (AICARFT).[2] Pemetrexed gains access to the cell via the reduced folate receptor and undergoes polyglutamation enhancing its activity.

Preclinical and clinical studies have shown that pemetrexed is active in a variety of cancers.[3] The recommended dose for pemetrexed as a single agent, given three weekly is 500–600 mg/m^2 with neutropaenia,[4] diarrhoea and mucositis being the dose-limiting toxicities. Single agent activity in a variety of common solid tumours such as lung, colorectal, breast and pancreatic cancer has led to further studies combining pemetrexed with platinum-based therapy or with gemcitabine. Interestingly, combination chemotherapy in these diseases can be given safely without the need to comprise the dose of either agent. There are good preclinical data to show that dietary folate supplementation reduces toxicity without affecting anti-tumour activity. It has been harder to demonstrate this in clinical studies, but there is indirect evidence that toxicity is increased in patients with a low folate status, so that folic acid and Vitamin B12 are now routinely given with pemetrexed, and dexamethasone is commonly used to reduce the incidence of skin toxicity. Following pivotal phase III trials, pemetrexed has been licensed for use in combination with cisplatin in pleural mesothelioma,[5] for non-small cell lung cancer with non-squamous histology,[6] and as second-line monotherapy for this subtype of non-small cell lung cancer.[7]

Thus far, there has been very little published information on the activity of pemetrexed in ovarian cancer but it is an interesting tumour to study as ovarian cancer responds to a broad range of anti-cancer drugs. Increased levels of folate receptor (a) are found on ovarian cancer cells,[8] although preclinical studies suggest that the reduced folate carrier (RFC) protein plays a more important role in antifolate transport.[9]

In the issue of the European Journal of Cancer, Vergote et al.[10] are the first to study the activity of pemetrexed as a single agent in ovarian cancer. They performed a randomised study, comparing a thrice weekly treatment with 500 mg/m^2 or 900 mg/m^2, a dose that was higher than in earlier phase II studies. In 102 patients with platinum-resistant disease, the overall response rate measured 9.3%, with no suggestion that a higher dose was more effective. Other clinical studies of single agent anti-folate therapy such as high-dose methotrexate, ralitrexed and ZD9331[11–13] have been equally and surprisingly disappointing, given the chemosensitivity of ovarian cancer, and known responses in this setting to gemcitabine, etoposide, topotecan and of course platinum or paclitaxel given again.

As a result of the encouraging data combining pemetrexed with other chemotherapeutic agents in mesothelioma and lung cancer, phase II studies have been performed in ovarian

cancer. Matulonis et al.[14] have recently published a phase II trial combining pemetrexed and carboplatin in patients with 'platinum-sensitive' relapse. High response rates were to be expected in this population, and the overall response rate of 51.1% in 44 patients was in keeping with the predicted outcome. The side-effects using pemetrexed 500 mg/m^2, thrice weekly, were acceptable although additional pemetrexed-related toxicities were seen. Twenty-nine percent of patients required a reduction in the dose of pemetrexed and this also involved compromising the carboplatin dose. A phase I dose escalation study of pemetrexed and gemcitabine was performed in women with recurrent ovarian cancer.[15] Doses of up to 600 mg/m^2 pemetrexed and 1500 mg/m^2 gemcitabine were given twice weekly with acceptable toxicity, and responses were reported in 24% of patients, all of whom had platinum-resistant disease.

The key question arising from these studies is whether the activity of pemetrexed should be pursued further in ovarian cancer, and if so, how this should be taken forward. Recurrent ovarian cancer is a heterogenous disease and tumours have been simplistically classified as 'platinum-sensitive' or 'platinum-resistant' on the basis of historical data, depending on the likelihood of responding to re-challenge with platinum therapy.[16] This means that any meaningful study incorporating a new compound with another drug must be undertaken in the context of a randomised trial. Measuring outcome on the basis of a CA125 response[17] may increase the ease of selecting patients for these studies as patients with non-measurable disease can be included, but the number of patients required to demonstrate differences in response or progression-free survival is quite considerable. An adaptive randomised phase II design (reviewed by Lee and Feng[18]) would provide a simpler mechanism of identifying promising agents to take forward into larger studies. These larger trials, whether led by industry or academic collaborations, are a major undertaking and have to be based on sound preliminary data.

Better selection of patients that are likely to respond to new drugs is urgently needed. In spite of 60 years of research with antifolates and the considerable knowledge on folate-dependent pathways, it remains difficult to identify clinically relevant biochemical markers of response; initial optimism in a number of studies has not been confirmed in larger trials. In ovarian cancer the construction of drug trials to address important therapeutic questions is particularly complex, as the positioning of an active agent in combination with other drugs in the treatment pathway needs careful consideration. Until better markers of sensitivity to pemetrexed are identified it is difficult to see how this agent will have a significant impact on the treatment of ovarian cancer.

Conflict of interest statement

None declared.

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Available online 4 March 2009

0959-8049/$ - see front matter

doi:10.1016/j.ejca.2009.02.006