Meeting report

Gemcitabine: novel combination of efficacy and tolerability

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Chemotherapy for many common solid tumors remains unsatisfactory and there is an urgent need for new agents with improved efficacy, balanced with greater tolerability which may improve performance status and symptom relief. Health economic benefits may also be required before emerging new anti-cancer drugs are accepted by health care providers. This was the background against which Professor Maurizio Tonato (Perugia, Italy) introduced a symposium on gemcitabine, a novel nucleoside analog against solid tumors.

The novel preclinical profile of gemcitabine was described by Dr William Plunkett (Houston, TX, USA). Gemcitabine differs from the natural nucleoside precursor deoxycytidine in the substitution of two fluorine atoms. Gemcitabine diphosphate exerts its cytotoxic action by inhibiting ribonucleotide reductase (the principal enzyme in the formation of deoxynucleotide triphosphates for normal DNA synthesis). Gemcitabine triphosphate competes with normal deoxycytidine triphosphate for incorporation into DNA. Once it has been incorporated into DNA, gemcitabine triphosphate is difficult to excise (due to a novel mechanism of masked chain termination) and blocks further DNA synthesis. Gemcitabine is also unusual because it self-potentiates its own activity. Based on its pharmacology, Dr Plunkett suggested that gemcitabine may be an ideal candidate for combination therapy because it is likely to potentiate radiation therapy and drugs that damage DNA.

Professor Raymond P Abratt (Cape Town, South Africa) reviewed single-agent response rates of 15–20% for the most active commercially available single agents in advanced non-small cell lung cancer (NSCLC): cisplatin, vindesine, ifosfamide and mitomycin C. Two-drug combinations produce higher response rates although survival benefit is marginal. Three-drug combinations do not appear to confer any further advantage. Dr Abratt pointed out that when choosing chemotherapy for the patient, the likely response rate and survival benefit must be balanced with toxicity. Future progress is most likely to be achieved with new agents alone or in combination with existing cytotoxics.

Professor Frances A Shepherd (Toronto, Canada) reviewed the single-agent efficacy of gemcitabine in NSCLC and small cell lung cancer (SCLC). In the phase II trials gemcitabine was given as a 30-min infusion, once a week for 3 weeks with a week of rest, at starting doses of 800–1250 mg/m^2. All gemcitabine responses were independently reviewed by an Oncology Review Board and only the validated responses have been reported. In the three most recent studies in advanced NSCLC (stage IIIa, IIIb and IV), response rates ranged from 20 to 22.5%. The poor response rate (3%) seen in the first study could be related to the lower doses and number of cycles administered. Following confirmation of the clinical activity against NSCLC, gemcitabine is now being studied in combination with cisplatin, vindesine, carboplatin and ifosfamide.

Professor Tonato summarized the safety data for up to 790 patients in the phase II study program. Hematological, liver and renal toxicity was usually mild, easily reversible and rarely dose-limiting. Hematological toxicity was particularly low with WHO grade 4 toxicities (by patient) of only 0.9% hemoglobin, 0.5% leukocytes, 5.7% segmented neutrophils, and 1.0% platelets. Myelosuppression typically did not require hospitalization. Nausea and vomiting were generally mild (WHO grades 3 and 4 were 19.8 and 0.9%, respectively), rarely dose-limiting and controlled by standard anti-emetics. Flu-like symptoms were reported but were generally mild (responsible for discontinuation in only one of 790 patients, 0.1%), short-lasting and rarely dose-limiting. Edema was responsible for discontinuations in six of 790 patients but was not associated with any evidence of cardiac, hepatic or renal failure. Professor Tonato emphasized that this non-overlapping toxicity, together with its novel mechanism of action, made gemcitabine a logical candidate for trial with other cytotoxic agents.

Dr William P Steward (Glasgow, UK) reinforced the rationale for combining gemcitabine with other anti-cancer drugs. In addition to gemcitabine's single-agent activity and tolerability, preclinical studies have shown that gemcitabine may enhance cytotoxicity of agents such as cisplatin by impairing DNA repair mechanisms. Dr Steward reported on the interim results of two gemcitabine combination studies, one with cisplatin and the other with vindesine. Preliminary data indicate significant activity and good tolerability.

Dr Nicholas Thatcher (Manchester, UK) challenged the prejudice that patients' performance status and quality of life always deteriorate with chemotherapy. A number of randomized trials have shown improvement in performance status with chemotherapy. A review of the gemcitabine database showed that symptoms improved in over half the patients. These improvements were obtained without the use of supportive measures such as steroids.

Dr Joseph Zammit-Lucia (Cambridge, UK) presented data based on the German health care system which suggested that gemcitabine monotherapy has the potential to generate considerable savings compared with an ifosfamide/etoposide combination in the management of inoperable stage III and IV NSCLC. These savings would be achieved through a reduction in hospitalization costs and a decrease in adverse events.

Dr Kurt Possinger (Berlin, Germany) reported an independently validated response rate of 32% in advanced breast cancer. The toxicity profile of gemcitabine was mild and predominantly non-hematological and did not overlap significantly with other cytotoxic agents used in breast cancer.

Dr Mogens Hansen (Hillerød, Denmark) reviewed a study of gemcitabine in ovarian cancer patients who had been previously treated with cisplatin, in which the independently validated response rate was 23% with modest hematological and non-hematological toxicity.

In his concluding remarks, Professor Abratt noted the reproduceable activity seen with gemcitabine, expressed confidence in the response rates derived of independent validation by Oncology Review Boards, and highlighted the remarkably low toxicity of gemcitabine, especially in lung cancer.