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Summary

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In early preclinical trials gemcitabine, a nucleoside analogue, showed impressive activity against a wide range of murine solid tumour and human xenograft models.

Further study of its pharmacology disclosed a number of multiple and novel mechanisms of action. Gemcitabine exerts its cytotoxic activity by (1) inhibiting ribonucleotide reductase, which leads to reduced incorporation of deoxynucleotides into DNA; and (2) acting as a competitive substrate for incorporation into DNA, where it leads to chain termination. This aspect of its pharmacology is particularly interesting because the gemcitabine nucleotide, which is substituted in place of deoxycytidine, allows one more nucleotide to pair before DNA chain replication is halted. This means that the gemcitabine nucleotide is less easily detected and excised by "proof-reading" exonuclease enzymes. This process is known as "masked chain termination", and is believed to be unique to gemcitabine.

A series of self-potentiating mechanisms are important both in increasing the activation of gemcitabine (by phosphorylation to the active nucleotides) and in decreasing the clearance of gemcitabine from the cell. These mechanisms explain why the intracellular accumulation and retention of gemcitabine is higher than that seen with ara-C, and hence why gemcitabine is more active in solid tumours.

Several dose schedules were evaluated in phase I trials. In a daily schedule (MTD 12 mg/m^2) the dose-limiting toxicities were flu-like symptoms, fever, malaise, headache, and in some patients, idiosyncratic episodes of severe or life-threatening hypotension. In a twice-a-week schedule (MTD 65 mg/m^2) the dose-limiting toxicity was thrombocytopenia. In a schedule in which gemcitabine was dosed every other week (MTD 4560 mg/m^2) the dose-limiting toxicity was myelosuppression—although it was possible to deliver high doses, little efficacy was observed, and this finding was supported by pharmacological studies which suggested that more frequent administration of less drug is required. These 3 schedules were not pursued in later studies. Instead, a weekly schedule was selected for the phase II studies. In this schedule, gemcitabine given in a cycle, once a week for 3 weeks followed by a week of rest, provided a combination of activity and acceptable tolerability with dose-limiting thrombocytopenia at 1000 mg/m^2.

The effects of escalating the dose and dose duration of gemcitabine are currently being investigated in a second generation of phase I trials. In one set of studies the approach has been simply to increase the dose of gemcitabine delivered within the 30 minute infusion period. In the other set of studies both the dose and duration of infusion have been increased proportionately in order to maintain a constant rate of dosing (10 mg/m^2/min).

One characteristic of the phase II clinical development programme is that gemcitabine has been studied in resistant solid tumours. Another feature of this programme is that the response rates are conservatively estimated in terms of all the responses having been reviewed by an Oncology Review Board (ORB). It is worth noting that the response status of some patients whom the investigators may have considered to have benefited from treatment will have been downgraded by the ORB or considered non-evaluable, and the overall response rate will have been reduced. This external review will help ensure activity in widespread clinical use.

In advanced non-small cell lung cancer (NSCLC) there are good data from a large pool of 361 patients that gemcitabine has reproducible activity. In the three largest NSCLC trials, gemcitabine produced response rates of 22.5%, 20% and 21.8% (all inde-

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pendently evaluated). These response rates are seen in all cell types and disease stages and place gemcitabine amongst the most active single agents against NSCLC. In addition to the objective response rates observed, gemcitabine was associated with an increase in performance status (in one-third of patients) and sustained improvements in a range of disease-specific symptoms such as cough, haemoptysis, pain, dyspnoea and anorexia. Besides its activity, gemcitabine has remarkable low toxicity in NSCLC patients. This is particularly relevant clinically as the toxicity of current chemotherapy for NSCLC has resulted in some clinicians having reservations about its use for patients with advanced disease. Also, as we move into the era of adjuvant and neo-adjuvant chemotherapy, where we may not have a marker to assess response, an agent with low toxicity would be advantageous.

There is a sound pharmacological rationale for combining gemcitabine with other cytotoxic agents, particularly those that damage DNA. Gemcitabine is a particularly attractive candidate for combination with cisplatin since cisplatin causes cell death by producing DNA–protein crosslinks, and gemcitabine is known to inhibit DNA excision repair, which is one of the major mechanisms by which tumours are thought to become resistant to cisplatin. The early combination studies with gemcitabine are promising and we await the final results.

In platinum-resistant ovarian cancer gemcitabine shows activity (19% overall response rate) which is equivalent to that seen with paclitaxel, but achieves this with modest effect on toxicity profile.[1]

In advanced breast cancer patients, two-thirds of whom had received previous chemotherapy, gemcitabine produced an independently validated response rate of 25%.

The toxicity seen with gemcitabine is unusually mild for such an active agent, characterized as generally mild, reversible, easily manageable, and predominantly non-haematological. Any myelosuppression seen generally does not lead to clinically significant episodes of infection. It is unusual to see a cytotoxic agent with a modest effect on the traditional toxicities such as myelosuppression, nausea and vomiting, and alopecia. This non-overlapping toxicity profile provides a further rationale for the incorporation of gemcitabine into combination regimens.

The costs of adverse-event management are expected to be low, since hospitalization or aggressive treatment with supportive drugs are not usually warranted (e.g. for myelosuppression or nausea and vomiting), and this may also have health economic benefits. The safety profile allows gemcitabine to be used in an out-patient setting for improving patient comfort and convenience while lowering costs.

Reference

1. Trimble EL, Adams JD, Vena D, *et al.* Paclitaxel for platinum-refractory ovarian cancer: results from the first 1000 patients registered to National Cancer Institute Treatment Referral Center 9103. *J Clin Oncol* 1993; **12**: 2405–10.