**Guest Editorial -
Minisymposium:
Lung Cancer**

Low-dose gemcitabine in long infusion: When less is more

This issue of the Journal brings a small but important report on a clinical trial comparing gemcitabine in low dose in long infusion to standard brief infusion of a much higher dose of gemcitabine, in both arms combined with carboplatin, for advanced non-small cell lung cancer (NSCLC).^[1] It is clear that the trial was not powered to confirm significant differences in efficacy between the two treatment arms. Nevertheless, we can agree with the authors that treatment with low-dose gemcitabine in long infusion is effective for advanced NSCLC, has low toxicity, and is especially attractive for deprived patients for whom the costs of anti-cancer drugs present an important, and often unsurmountable barrier to treatment.

I would like to stress that treatment with low-dose gemcitabine in long infusion is much more than a simple reduction of costs for cytotoxic drugs. Gemcitabine in long infusion appears to be a different drug, when compared to standard gemcitabine in brief infusion. Long infusion leads to a much higher proportion of conversion of the drug into the active metabolite. As a consequence, maximal tolerated dose (MTD) for gemcitabine which is 1500mg/m² or even higher for a brief 20-30 min infusion falls with the duration of infusion. With infusions lasting for 3, 6 or 24hrs, MTD falls to 450mg/m², 250mg/m², and 180mg/m², respectively.^[2-5] In addition to lower MTD, long infusion of gemcitabine has a different toxicity profile. Our randomized trial on 249 patients with advanced NSCLC and treated with standard brief application or low-dose prolonged infusion of gemcitabine revealed significantly less neutropenias and thrombocytopenias for the prolonged-infusion arm; on the other hand, most of these patients developed alopecia, a side effect which is rare with standard brief infusion of gemcitabine.

The most important aspect of treatment with low-dose gemcitabine in prolonged infusion is its efficacy against

a variety of tumors. According to reports from other centers, gemcitabine in prolonged infusion alone or in combination with other drugs is an active treatment for advanced cancers of the breast,^[3,6] lung,^[7-10] refractory Hodgkin's disease,^[11] sarcomas,^[12] cancer of pancreas, gallbladder and biliary tract,^[13-16] and bladder cancer.^[17]

At the Institute of Oncology in Ljubljana, Slovenia, we have probably the largest experience on this treatment. Over the past 10 years, a total of 547 patients with NSCLC, with mesothelioma, and a few with other refractory cancers were enrolled in six prospective clinical trials and treated with low dose gemcitabine in prolonged infusion.^[18-21] Our experience can be summarized in the following points:

- Treatment with gemcitabine at 250mg/m² in 6hrs infusion and cisplatin (75mg/m²) leads to remarkable remissions in lung cancer and in mesothelioma [Figures 1 and 2]. The efficacy of this treatment is at least as good as, and possibly superior to standard brief infusion of gemcitabine. Superiority of the low-dose prolonged-infusion schedule is especially clear for patients with squamous-cell NSCLC (survival advantage two months, when compared to brief high-dose infusion)^[19] and for mesothelioma (17 months as median survival for unselected group of patients, including patients in poor performance status).^[21] In addition, partial remissions were seen in patients with pre-treated metastatic cervical cancer and head and neck cancer (unpublished observations).
- For the low-dose gemcitabine in long infusion, no clear dose-response relation is apparent. In our first trial with escalating doses of gemcitabine, we saw a complete response in one of six patients treated at the lowest level of 130mg/m²/6hrs.^[18]
- Apart from alopecia, toxicity is very mild. Gemcitabine at 150-200mg/m²/6hrs, alone or in combination with cisplatin or carboplatin is a suitable treatment for patients in poor performance status.^[20]

On the basis of current experience with low-dose gemcitabine in long infusion, we can say that this treatment is effective and safe. Future development will probably lead in two directions. The first one is based on low costs of this particular treatment. The second one is clinical research on potential superiority of this treatment against standard treatment for a variety of advanced cancers.

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Table 1: Comparison of different schedules of gemcitabine

Schedule	Dose rate (mg/m ² /min)	Comparison to standard schedule		References
		Efficacy	Toxicity	
1250 mg/m ² /20 min	62	Standard schedule		
1000 mg/m ² /100 min	10	Same	Same	8
350 mg/m ² /4 h	1.5	Same	Lower	1, 10
250 mg/m ² /6 h	0.7	Better for squamous NSCLC and mesothelioma; promising activity against many other cancers, but not confirmed in controlled clinical trials	Lower	6, 7, 11-18, 21, 22
150-200 mg/m ² /6 h	0.4-0.55	Recommended schedule for future clinical trials

Figure 1: Epithelioid mesothelioma of the left pleura, T3 N2 M0, prior to treatment

Figure 2: Complete remission three months after treatment with gemcitabine (130 mg/m²/6 hours on days 1 and 8) and cisplatin (75 mg/m² on day 2)

Low costs of anti-cancer drugs are an important parameter in clinical decisions, especially in economically deprived patients. Reduction of gemcitabine to 25% of the standard dose presents important savings. In addition, four hours infusion of gemcitabine, followed by carboplatin can be completed in a single day and is a suitable regime for out-patient treatment. This may be an important advantage of the schedule used by Beniwal SK *et al.*,^[1] when compared to our schedule which is divided between two days: six hours infusion of gemcitabine on day one, followed by cisplatin on day two. However, apart from reduction of costs, other advantages of the 4hrs infusion of gemcitabine over standard brief infusions are uncertain.

Research on new indications and on potential superiority of low-dose gemcitabine in long infusion is a challenge for future clinical trials. Candidates for clinical trials are patients with NSCLC (especially squamous type), mesothelioma, pancreatic carcinoma, breast cancer, advanced cancer of head and neck, esophageal cancer, and cervical cancer. When it comes to clinical trials, we should explore the optimal schedule of application, rather than a compromise made due to easier logistics. On the basis of all existing experience, I strongly believe that the

advantage of low-dose gemcitabine can be expected only with infusion duration of at least 6hrs [Table 1]. Use of infusion pumps is mandatory to control the duration of the infusion. The optimal dose of gemcitabine is less clear. For a 6hrs infusion, the dose should not exceed 250mg/m² but lower doses of 150-200mg/m² may be equally effective, as seen in our Phase 1-2 clinical trial of escalating doses of gemcitabine for NSCLC and in our trial for mesothelioma.^[21] Finally, aiming at optimal results, the doublet should include cisplatin, rather than carboplatin. As explained, the doublet of gemcitabine in 6hrs infusion and cisplatin with appropriate antiemetics and hydration is usually divided between two days. While this involves some logistics and costs for additional transport or hospitalization, I believe that the effort is justified if superiority of this treatment is to be confirmed.

Design, organization and performance of clinical research which is not commercially interesting is a challenge which invites brave, dedicated and enthusiastic physicians. From the experience of our team in Ljubljana, I can testify that even without commercial sponsorship, the task is feasible and

scientifically and personally rewarding. Less is more-a new challenge for Indian oncologists.

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