Continuous infusional 5-fluorouracil in breast cancer or the revival of an old drug?

Sometimes the old drugs may still be the best. 5-Fluorouracil (5-FU) was synthesised by Heidelberger in 1957 [1] and quickly went into clinical trials. Despite all the subsequent developments in cancer chemotherapy, it is still our most widely prescribed cytotoxic drug, mainly because of its central role in GI malignancies and in combination chemotherapy for breast cancer. Ironically 40 years later we still do not know the best way to use this drug.

5-FU is the classic example of a cycle specific S-phase dependent drug with a short half life of 10–20 minutes [2]. It is therefore reasonable to postulate that conventional bolus injection, however pragmatic, may well not be the most effective schedule. Many other regimens have been investigated; one of the most interesting has been the development of long-term continuous infusional therapy. This is by no means new [3], but interest in the technique has grown in recent years with the development of ambulatory pumps and long-term indwelling central venous catheters. Lokich, a pioneer of infusional 5-FU, established that surprisingly large doses of up to 300 mg/m$^2$ per day could be delivered in this way for prolonged periods (a greater than 6-fold increase in dose intensity over standard CMF), with plantar-palmar syndrome and mucositis replacing myelosuppression as the dose-limiting toxicity [4]. He subsequently went on to demonstrate in a randomised trial in colorectal cancer that continuous infusional 5-FU for 10 weeks or more achieved a significantly higher response rate than 5 day conventional bolus treatment (30% versus 7%) with less myelosuppression [5].

In breast cancer, a series of small phase 2 studies of continuous infusional 5-FU has recently been reviewed, with an overall response rate of 29% [6]; there was wide variation between individual studies, including one with a response rate of 54% [7]. Most of these patients had been heavily pretreated, and this frequently included conventional 5-FU.

The largest and most detailed of such studies is reported in this issue of Annals of Oncology by Regazzoni et al. from Lugano [8]. One hundred six consecu- tive patients with advanced breast cancer who had failed previous chemotherapy were treated with outpatient infusional 5-FU 250 mg/m$^2$ every 24 hours for 3-week periods followed by 1 week pauses. For most of these patients this treatment represented third-line chemotherapy. In a retrospective analysis 17 patients (21%) of 80 evaluable achieved a formal objective response, and a further 29% had stable disease. This included a response rate of 20% for patients previously treated with conventional 5-FU. The median time to disease progression for this group was 259 days with a range of up to 737 days. The authors also reported subjective responses in 44% of 104 patients evaluable for this softer end-point; these included improvement in soft tissue disease, reduction in bone pain and improvement in dyspnoea. In general, treatment was well tolerated with a very low incidence of grade 2 and greater toxicities. The authors concluded that infusional 5-FU provided useful palliative benefit with low toxicity at a very advanced stage of breast cancer; living with the pump was the only problem for most patients.

What conclusions can be drawn from such retrospective data with their inevitable limitations? The clinician faced with the difficult problem of symptom control in heavily pre-treated patients with advanced breast cancer could well be tempted to try infusional 5-FU with little to lose in toxicity. The treatment is labour intensive, however, with the cost implications of a specialist back-up nursing staff which we certainly find essential for infusional chemotherapy on our Unit. More important, this study raises the question of whether there might be a real therapeutic gain with infusional 5-FU at an earlier stage in the management of breast cancer.

At the Royal Marsden, we evaluated infusional 5-FU 200 mg/m$^2$ per day continuously for up to 6 months, in combination with bolus epirubicin and cisplatin (so called infusional ECF) as first-line treatment in breast cancer, and found high activity. Eighty-six percent of patients with metastatic/locally advanced disease achieved an objective response including a 36% complete remission rate [9]. The schedule when used as pre-operative chemotherapy in 50 patients with large early breast cancer achieved a 98% objective response with 66% complete remissions [10]. We are currently running 2 multicentre randomised trials of this schedule against conventional chemotherapy, as primary/neoadjuvant treatment (versus doxorubicin/cyclophosphamide) and as adjuvant therapy (versus 5-FU, epirubicin and cyclophosphamide). Further trials are needed in these areas and also as front-line treatment for metastatic disease; in particular we need trials with infusional versus conventional 5-FU as the only variable.

It would also be of interest to see a randomised comparison of infusional 5-FU alone as first-line chemotherapy for the palliation of advanced breast cancer against conventional schedules with toxicity and quality of life measures in addition to the usual efficacy endpoints. Such a trial should not strive to achieve the
maximal dose of 5-FU, but one with activity and low toxicity. Phase 2 studies have so far failed to show clear evidence of a steep dose response [7, 11], and breast cancer badly needs an effective palliative chemotherapy treatment with minimal toxicity. In this respect, breast cancer can learn from colorectal cancer. A currently running trial of infusional versus conventional bolus 5-FU with leucovorin rescue as adjuvant treatment for colorectal cancer at the Royal Marsden is showing very marked reduction in subjective toxicity with the infusional arm (D. Cunningham, personal communication).

Finally, there may be an intriguing new twist to the infusional 5-FU story. Dihydropyrimidine dehydrogenase (DPD) is the first enzyme in a degradative pathway which rapidly reduces over 80% of systemic 5-FU [12]. It is found in a variety of human tissues, including the intestinal mucosa and may be in part associated with the unpredictable oral bioavailability of 5-FU. Potent inhibitors of DPD have been developed [13] which very significantly prolong the half-life and make the bioavailability of oral 5-FU much more predictable. Such agents, which are already in clinical trials, may allow the administration of long term low dose oral 5-FU with the same pharmacokinetic profile as continuous infusion, but without the resource implications or the hassle of the pump.

The Lugano Group’s study is another useful stimulus towards appropriately designed trials to assess the real value and role of continuous infusional 5-FU. The question should not remain unanswered for another 40 years.

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References