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Comments and Critique

Continuous, Hyperfractionated, Accelerated Radiotherapy (CHART)

IN A COURSE of radiotherapy, the radiation dose, number of individual treatments and overall duration are influenced by several factors, including the known radiosensitivity of the tumour, tumour size, the normal tissues included and the purpose of the treatment (palliation or cure). A wide range of schedules have been developed, based largely on clinical experience.

Many human tumours can rapidly repopulate and in some sites, such as the head and neck, at least half the squamous cell carcinomas can potentially double their cell number in 5 or fewer days [1–4]. The discrepancy between the cellular and the much longer volume doubling times seen clinically results from the high clonogenic cell loss due to degeneration and differentiation [5]. When there is cell destruction by radiotherapy, or by cytotoxic chemotherapy, the surviving cells repopulate rapidly. During a protracted course of radiotherapy over 6–7 weeks it is necessary, therefore, not only to destroy all tumour cells present at the beginning of therapy, but also all those that have resulted from cellular repopulation during the period of treatment. The administration of treatment in many small doses may spare the late changes in normal tissues due to radiotherapy, which appear several months or years later [1, 6].

To limit the repopulation of tumours a reduction in the overall duration of treatment should give benefit; however, to do so and to minimise late damage, more than one treatment must be given each day. Many clinical studies have used multiple treatments in 1 day [7]. The normal dose increment of 2 Gy cannot be used in an uninterrupted course of accelerated treatment without exceeding the tolerance of normal tissues [7]. To improve tolerance many radiotherapists have interrupted treatment for a rest period of 2–4 weeks [8, 9]. This, unfortunately, may allow considerable repopulation of the surviving tumour cells, before the final phase of treatment is given. Although "pure" hyperfractionated radiotherapy—treatment twice instead of once a day over 7 weeks—has yielded improved local control in a randomised trial, no significant benefit has yet emerged from any phase III studies of accelerated treatment although benefit has been seen in non-randomised trials.

At Mount Vernon Hospital a novel scheme of continuous, hyperfractionated, accelerated radiotherapy (CHART) was devised in which radiotherapy was given three times daily, with 6 hours between fractions, for 12 days (including one weekend). A pilot study was started in January 1985 and a dose of 1.4 Gy was given to the first 38 patients (minimum tumour dose 50.4 Gy). As tolerance appeared good, the dose was increased to 1.5 Gy (total dose 54 Gy) [10].

Early radiation reactions were severe, but generally well tolerated. In some cases final healing of small areas has been delayed several months, but all these lesions have resolved. Radiation myelitis was an unexpected complication in 4 patients; as a result the radiation dose to the spinal cord has been reduced and no further cases have presented [11]. Late normal changes in other tissues have been less than expected. Hair grew in skin given full radiation dose and salivary function recovered to a greater extent than after conventional radiotherapy [11].

In the pilot study there were 92 patients with squamous carcinomas in the major sites in the head and neck. In a matching study with previously treated cases [12], life-table analyses showed that in the 71 patients with T3 and T4 tumours there was primary tumour control in 63% of cases at 2 years compared with 39% in the previously treated group ($P = 0.0001$); at 2 years, survival was 56% compared with 44% ($P = 0.05$). The results in 75 patients with primary bronchial non-oat cell carcinoma were compared with a previous group of 62 patients with similar tumours [13]. Clearance has been obtained in 40% compared with 16% in the previous group; at 2 years, survival of 32% can be contrasted with 12% previously ($P = 0.01$).

After consideration of these findings, a joint Medical Research Council, Cancer Research Campaign and Department of Health initiative has resulted in the establishment of multicentre randomised trials in these two main tumour sites. The trials fully opened in March 1990 and by July 1990 five centres in the UK and one in Dresden in Germany had randomised, in all, 88 cases. Five further centres are due to enter cases before the end of the year. If, in these randomised studies, CHART is shown to be superior to conventional radiotherapy then this will provide strong evidence that cellular repopulation does occur, at least in some human tumours, which will have significance for the whole of oncology. All treatment planned for a patient, whether it be surgery, radiotherapy or cytotoxic chemotherapy, will need to be given in the shortest overall period possible to minimise cellular repopulation as a cause for failure.

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What Can We Expect from Myeloid Growth Factors?

THE USE of myeloid growth factors in cancer patients has two important aims: (a) by reducing the period of neutropenia, these factors can significantly decrease the morbidity associated with conventional chemotherapy (e.g. by decreasing the number of severe infections and the frequency and severity of mucositis); and (b) by allowing more intensive chemotherapy regimens, these factors might improve response rates and survival [1].

Granulocyte–macrophage colony-stimulating factor (GM-CSF) and granulocyte colony-stimulating factor (G-CSF) are the two main myeloid growth factors. In the past few years, the availability of recombinant human (rh) versions of these agents has allowed animal and clinical testing. Despite their similar names, an historical consequence of the same *in vitro* colony assays being used for initial identification, the factors differ biologically and clinically. They have different molecular structure, cell membrane receptors, and target cells—G-CSF more selectively stimulates granulocyte and, to a lesser extent, monocyte precursors, while GM-CSF also affects eosinophils, macrophages and, at least *in vitro*, platelets. Moreover, the genes for these factors are located on different chromosomes (chromosome 5 for GM-CSF and chromosome 17 for G-CSF). Finally, GM-CSF and G-CSF have different effects on neutrophil kinetics [2]. Several phase I/II studies have now been reported. Both agents increase leucocyte numbers in patients before and after chemotherapy [3]. Non-randomised studies suggest a clinical benefit in terms of a reduction of the often severe neutropenia that follows cytotoxic chemotherapy. GM-CSF can cause mild fatigue, weakness, fever, anorexia and transient dyspnoea; at higher but clinically unnecessary doses it can also cause more severe side-effects such as thrombosis, effusions, hypotension and respiratory distress. G-CSF appears to be less toxic, and no maximum tolerated dose has been clearly identified, although rhG-CSF can cause, like GM-CSF, musculoskeletal pains in a small proportion of patients.

GM-CSF appears to act mainly locally, in a "paracrine" fashion, leading to local activation of granulocyte and macrophage function, including stimulation of antitumoral cytotoxicity. G-CSF, on the other hand, can also be detected in the circulation, and serum levels increase following endotoxin stimulation or infection and inflammation, thus behaving more like a "granulopoietin".

Dr Biesma and colleagues (p. 932) report the first double-blind placebo-controlled trial of rhGM-CSF in the treatment, rather than prophylaxis, of chemotherapy-related leukopenia and fever without bone marrow transplantation. Disappointingly, GM-CSF did not shorten the period of fever or antibiotic administration. More placebo-controlled studies of this kind are needed to confirm this negative result, perhaps with a higher dose and earlier administration of rhGM-CSF. It is also possible that at higher doses the toxicity of GM-CSF, which was negligible in this study, will become more important. No similar study has yet been reported for rhG-CSF, but it is clear from phase II and randomised phase III studies (in patients treated with conventional-dose chemotherapy) that G-CSF administered prophylactically significantly reduces the frequency of febrile neutropenia and allows chemotherapy to be administered on schedule [4]. Furthermore, in a preliminary analysis of a study by Morstyn *et al.* [5] in the treatment, rather than prophylaxis,