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Perspectives and Commentaries

Optimal Schedule for Anthracyclines

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(A COMMENT ON: Weenen H, Pinedo HM, de Planque MM, ten Bokkel Huinink WW, MvVie JG, Lankelma J. Pharmacokinetics of carminomycin in man: biweekly schedule vs single dose every three weeks. *Eur J Cancer Clin Oncol*, 1984, **20**, 915–918.)

THE ANTHRACYCLINES, and in particular doxorubicin, are amongst the most active agents in cancer chemotherapy. They are nearly always used on an intermittent, relatively high-dose bolus injection schedule at 3-week intervals. This approach is certainly associated with a wide spectrum of anti-tumour activity but toxicity is considerable: myelosuppression, nausea and vomiting are common, alopecia is almost inevitable and cumulative cardiotoxicity is eventually dose-limiting. In this journal a Dutch group report on the pharmacokinetics of carcinomycin, a doxorubicin analogue, given in different schedules and rightly question whether a 3-week regimen is always the optimal way of using anthracyclines [Weenen *et al.*].

This schedule was developed in the early 1970s, based partly on pharmacokinetic principles [1] and partly on clinical pragmatism. The pharmacokinetics of the anthracyclines are quite distinctive and are characterised by rapid tissue uptake and prolonged binding. Thus doxorubicin shows a triphasic plasma half-life, the first phase of which is short (10–13 min) and largely represents tissue uptake; the second phase half-life is around 10 hr and mainly represents drug metabolism; the third phase is prolonged, at around 24–48 hr, and represents slow release from multiple sites of tissue binding [2]. This long terminal half-life provides some justification for a 3-week scheduling [1], but clinical factors have also proved relevant. First, early phase II studies demonstrated that 3-day courses of treatment or prolonged low-dosage therapy were associated with unpleasant mucositis which could be markedly diminished with an intermittent 3-week schedule [3, 4]. Second, a 3-week schedule allowed full recovery from a pattern of myelosuppression which had a nadir around 10–12 days after treatment [4]. Finally, the convenience for patients of a treatment given once every 3 weeks compared with more frequent scheduling was quickly appreciated.

Despite these arguments, attention has begun to focus again on other schedules. One group [5] reported that doxorubicin in a low dose of 20 mg/m^2 on days 1 and 8, repeating every 28 days, achieved tumour regressions in 27% of patients with advanced breast cancer resistant to conventional chemotherapy; toxicity was relatively mild with minimal myelosuppression, occasional vomiting, hair loss in only one-third of the patients and no cardiotoxicity. Another group [6] recently compared the same dose weekly to 60 mg/m^2 every 3 weeks in a randomised trial of combination chemotherapy for non-small cell lung cancer. The low-dose weekly regimen was as effective as conventional scheduling in terms of response rate and survival but was associated with significantly less neutropenia, infection and cardiotoxicity as assessed by left ventricular ejection fraction and endocardial biopsies. This last observation was particularly impressive given that five patients on a weekly scheule received a cumulative dose of 740–1190 mg/m^2 whereas none on the 3-week schedule received more than 550 mg/m^2.

Even lower doses of doxorubicin (6–12 mg/m^2) have been reported as achieving objective responses in 20 of 35 patients with advanced breast cancer (57%), with a median response duration in

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excess of 12 months [7]. Sixteen patients had previously received adriamycin in a conventional dosage including 12 with cumulative doses of 520–550 mg/m². Toxicity was minimal: no myelosuppression, mucositis, vomiting or cardiotoxicity was seen (even in 14 patients receiving a total dose of 700–1030 mg/m²); alopecia requiring a wig occurred in only two (6%) patients. More recently the same group have reported that this regimen has the same anti-tumor efficacy as a combination of 5-FU, cyclophosphamide and conventional doxorubicin in a randomised trial [W. Mattsson, personal communication]. Based on these studies, Jones and Mattsson [8] have investigated low-dose weekly 4-epidoxorubicin, a new doxorubicin analogue. Again a high response rate (51%) with minimal toxicity was reported.

Another approach to alternative anthracycline scheduling has been the investigation of continuous low-dose doxorubicin infusions, sometimes by ambulatory pumps, for periods of 48 hr to 60 days (several groups, e.g. [9–11]). Again these studies have consistently demonstrated significantly less cardiotoxicity as assessed by cardiac biopsy and gated pool scans. Other side-effects including nausea, vomiting and alopecia also appear to be very markedly reduced, although stomatitis and leukopenia have been seen at higher doses [9, 11]. Objective tumor responses have been achieved, although comparisons with conventional scheduling are difficult since many patients had received previous chemotherapy. The pharmacokinetics of low-dose weekly or continuous infusion therapy are by no means fully worked out, but some data are available. The Dutch group writing in this journal [Weenen *et al.*] showed that the terminal plasma half-life of the metabolite carminomycinol was significantly prolonged with successive injections of low-dose carminomycin and another study reported that frequent (8-hourly) injections of low-dose doxorubicin were associated with a loss of rapid initial plasma clearance into tissues and gradual accumulation in plasma [12]. It has also been suggested that at a low dosage (15 mg/m²) plasma clearance of doxorubicin may follow a biphasic rather than a triphasic profile with prolonged plasma levels [13]. Clearly, while total concentration × time ($c \times t$) may or may not change significantly with different schedules, the most striking pharmacokinetic feature of any low-dose therapy must be that initial peak plasma levels are very much lower than those obtained with conventional treatment.

This is the most interesting aspect of low-dose scheduling. These clinical studies, if confirmed (and confirmation remains essential here), suggest that peak plasma anthracycline levels may be much more critical for some tissues than for others. If low-dose weekly or continuous infusion therapy really has similar efficacy to conventional treatment, then tumor tissues would not appear to be influenced so much by peak plasma levels as perhaps by $c \times t$. Certainly bolus high-dose anthracycline treatment has in general been disappointing as an area of clinical research. The same may be true for digestive tract mucosa; there is the recurring impression that stomatitis is more of a problem with prolonged treatment than with intermittent bolus therapy. In striking contrast, a close correlation appears to exist between peak plasma and toxicity to hair follicles, to myocardium, probably to bone marrow and to the chemoreceptors triggering vomiting. Here toxicity seems consistently and strikingly greater with high-dose intermittent scheduling than with low-dose therapy. Why this should be is not clear; one hypothesis postulates that the existence of an active excretory pump mechanism for removing adriamycin from cells in some tissues (e.g. myocardium) but not others could explain this differential protective effect [14].

Given the greater inconvenience of weekly or continuous infusion therapy, does any of this really matter if different schedules are not going to influence anti-tumour effect in any major way? The answer is almost certainly yes. In the short term, alopecia, nausea and vomiting are distressing side-effects, particularly with palliative treatment, and undoubtedly these restrict the use of doxorubicin, for example, in advanced breast cancer. In the long term, cardiotoxicity may prove as important a problem. Overt cardiac failure during treatment can be minimized by a cumulative doxorubicin dose restriction to 550 mg/m², but subclinical cardiac damage occurs at a much lower dosage and abnormal cardiac function has been shown to persist without improvement several years after treatment [15]. Long-term sequelae can only be guessed at, but this uncertainty has restricted the use of the anthracyclines in potentially curative treatment including adjuvant chemotherapy or in Hodgkin's disease.

For several years now attempts to develop less toxic (and in particular less cardiotoxic) anthracycline analogues with an efficacy equal to that of doxorubicin have met with failure. It may be that the answer, at least in part, lies simply in designing better schedules for existing anthracyclines. Further trials are certainly warranted.

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