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Dose-response Relationships in Testicular Cancer

FEW TOPICS in chemotherapy have received as much attention in recent months as the interrelation of dose, dose intensity and response. The imminent possibility of using growth factors to ameliorate the myelosuppressive consequences of higher dose chemotherapy has fuelled this debate. Looking back it is disappointing that, with a few exceptions, the clinical studies examining dose effects have not been designed optimally to resolve the issues addressed.

Non-seminomatous germ cell tumours (NSGCT) provide an excellent model for testing questions of dosage since not only are they very chemotherapy-sensitive, but prognostic factors identifying categories of patient at higher risk of failure are well worked out. An early trial addressing dose-response and survival came from the Southwest Oncology Group [1]. 114 patients with advanced testicular cancer were randomised to high-dose cisplatin (120 mg/m^2) or low-dose cisplatin (75 mg/m^2), both with vinblastine and bleomycin. The trial included patients with all stages of metastatic NSGCT and in addition a few cases of pure seminoma. Unfortunately the schedule of cisplatin administration was different between the two arms as well as the total dose. In the high-dose arm the cisplatin was given all on 1 day, whereas the low dose cisplatin was fractionated over 5 days. Although this may not have influenced the final result (a significant response and survival benefit for the high-dose arm) there is no very good reason in the paper why the trial was complicated in a way that combines schedule and dose variables so that their independent effects are obscured.

The next attempt to look at dose effects in NSGCT was from the US National Cancer Institute. In this trial, reported by Ozols *et al.* [2], 52 poor prognosis patients were randomised to receive cisplatin, vinblastine and bleomycin (PVB) or double dose cisplatin (200 mg/m^2) with vinblastine, bleomycin and etoposide. The results clearly favoured the double dose cisplatin arm, apparently in support of the concept of dosage intensity. Unfortunately again, there was more than one variable in that the high-dose arm also included etoposide. Independent evidence from Williams *et al.* [3] had already shown that the substitution of vinblastine in PVB with etoposide was associated with a survival advantage in poor prognosis patients.

The definitive trial of cisplatin dose intensity, i.e. a trial in which the only variable was the dose of this, the most active single agent in NSGCT, was reported in abstract form last year [4]. 153 assessable patients with poor prognosis disease were randomised to receive either 4 courses of standard cisplatin (100 mg/m^2), etoposide and bleomycin vs. high-dose cisplatin (200 mg/m^2), etoposide and bleomycin. The results were not significantly different except for toxicity which, not surprisingly, was greater in the high-dose arm. Other studies (e.g. that employing the POMB/ACE schedule from Newlands *et al.* [5]) have looked retrospectively at received dose intensity and concluded that patients given higher intensity therapy did better. Using the same regimen we found no such effect [6].

This present issue of the *European Journal of Cancer* includes a report from Villejuif of high dose chemotherapy with autologous bone marrow rescue in "refractory" germ cell cancer (p. 831). Here again there are confounding factors which obscure worthwhile conclusions. The study examines 17 heavily pretreated patients with refractory or relapsing NSGCT who were treated with cisplatin (200 mg/m^2), etoposide (1750 mg/m^2) and cyclophosphamide (6400 mg/m^2) over days 1–5, with autologous bone marrow transplantation (ABMT) on day 8. The majority of cases had already received and apparently failed high-dose chemotherapy with one or more of the agents in question; thus employing these again in the salvage regimen under study makes realistic conclusions very difficult. Furthermore, among the 4 long-term survivors there are 2 cases who were in complete remission when they entered the study. The implication from the paper's title is that the study treatment contributed to the long-term survival in these 4 patients. That is clearly not necessarily the case. On the other hand the conclusion stated in the abstract is that the regimen may be a useful consolidation treatment in patients responding to conventional salvage chemotherapy. This may be so but the work reported offers no data to support the conclusion.

There is a considerable body of evidence that, for the majority of chemotherapeutic agents, there is a steep dose-response curve when the agents are studied in *in vitro* and *in vivo* models. Consequently it is not surprising that high-dose chemotherapy with ABMT has been an attractive area of investigation for the treatment of solid tumours. In other tumours, as well as in testicular cancer, much of the data used to support the importance of dose and dose intensity is retrospective and thus confounded by other variables [7]. Indeed some studies find no correlation and still others addressing the same question are contradictory. Few randomised studies have solely and specifically addressed the question of drug dose. Those which did have generally been negative. Of course, if treatment has any effect in the tumour under study, then it will always be possible to choose a small enough dose level to be indistinguishable from no treatment and therefore demonstrate a dose-response effect. It is quite possible that dose-response curves may plateau at the "optimal" dose level, and that further relatively modest escalations contribute to extra toxicity only. In testicular cancer there is increasing evidence that long-term toxicity is dose-related [8]. At a time when it appears we may shortly be able to reduce substantially the immediate myelotoxicity of chemotherapy, it is very important we design studies carefully and thus avoid many of the flaws apparent in the reports that have appeared in the last decade. Indeed, one of the principal challenges for the nineties will be to properly address questions pertaining to the importance of dose in cancer chemotherapy. Economic as well as scientific pressures will demand this.

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Prophylaxis and Empiric Therapy for Streptococcal Infections in Febrile Neutropenic Patients

THERE HAS been a progressive change in the microbiological nature of bacterial infections in neutropenic patients. During the past decade, sepsis caused by gram negative pathogens has been replaced by infections due to gram positive organisms, namely various streptococcal strains.

This evolution poses new questions about the management of the febrile patient with granulocytopenia; time-honoured attitudes have to be evaluated again and new approaches towards prophylaxis and therapy must be designed.

Streptococcal septicaemia is frequent in both neutropenic adults and children (respectively, 20% and 40%, at least, of all cases of bacteraemia). The morbidity and the mortality attributed to these infections have been probably underestimated in the literature. Retrospective studies indicate mortality rates of approximately 10–15%. In addition, these infections are expensive in terms of use of antibiotics, nursing care, associated treatments, days of hospitalisation and overall suffering. Consequently, prophylaxis might have a critical role in patients exposed to clinical situations known to predispose to these infections.

A large scale prophylactic study is presently being conducted by the EORTC Antimicrobial Therapy Cooperative Group and has entered 700 patients to date. This double-blind investigation includes oral administration of pefloxacin, associated with either a placebo or penicillin V. Data from this EORTC study are not available so far but they will be instrumental in designing new therapeutic attitudes and/or studies. However, it should be stressed that while pneumococci are sensitive to penicillin V, this is not the case for all streptococci, and in particular *Streptococcus anginosus*, for which the minimum inhibitory concentrations (MICs) are 10 times higher. Penicillin resistant streptococci, as well as tolerance to penicillin by these organisms have been reported as well. As far as glycopeptides are concerned, a pilot study of healthy non-neutropenic volunteers used the oral administration of teicoplanin for 3 weeks [1]. In the stools, a marked rise was noted for staphylococci (*Staph. haemolyticus* and *Staph. epidermis*) with an elevated MIC to teicoplanin; the decrease in streptococci in the stools after the start of treatment was followed by an increase due to the selection of *Escherichia faecium*, and a high level of *E. faecium* was still detectable 1 week after the cessation of treatment. These *E. faecium* are potential carriers of an autotransmissible and inductible plasmids; the gene appears identical to that coding for resistance to vancomycin in *E. faecalis*.

The rise observed recently in the frequency of streptococcal septicaemia among neutropenic patients coincides with the increased use of quinolones—to which most streptococci are resistant—for prophylactic purposes, e.g. gastrointestinal tract decontamination. However, this emergence of streptococci has also been reported in institutions that do not use quinolones for prophylaxis and infections due to streptococci have become common on paediatric services where no quinolones are prescribed. Moreover, prophylactic trials comparing quinolones with a placebo have revealed similar rates of gram positive infections [2]. Thus, the avoidance of quinolones for prophylaxis of gram negative infections in granulocytopenia patients would probably not eliminate the problem posed by streptococci. Controlled trials comparing the efficacy of quinolones for the decontamination of the gastrointestinal tract with other regimens have demonstrated that quinolones can reduce significantly the frequency of gram negative infections. Other prophylactic approaches (cotrimoxazole, vancomycin–gentamicin, etc) but not quinolones can reduce the frequency of infections caused by gram positive pathogens as well. However, these regimens are much less well tolerated than quinolones.

Since the main sanctuaries for streptococci is the mucosa of the oropharynx (*Strep. mitis*, *Strep. sanguis*, *Strep. salivarius* and *Strep. anginosus*), of the gastrointestinal tract (enterococci) and of the vagina (*Strep. anginosus*) future research should investigate

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