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Perspectives and Commentaries

The Concept of Priming

J. L. MILLAR and T. J. McELWAIN
Section of Medicine, Institute of Cancer Research, Clifton Avenue, Sutton, Surrey, U.K.

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SEVERAL years ago Smith and her colleagues noticed that pretreatment with the stathmokinetic agents vinblastine, vincristine or colchicine 2 days before total-body irradiation reduced the bone marrow toxicity from radiation in mice [1, 2]. Independently Jeney and co-workers showed that small doses of merophan could diminish the toxicity of high doses of merophan and melphalan if they were administered 2 days before the high dose in rats [3]. Neither of these groups investigated the effect of these normal tissue sparing combinations on tumour tissue.

This pretreatment with low doses of cytotoxic drugs before high doses of cytotoxic drugs leading to normal tissue damage has been called 'priming'.

In 1975 members of this institute observed that two alkylating agents, namely cyclophosphamide and busulphan, produced less toxicity than busulphan used on its own in mice. To achieve optimum tissue sparing cyclophosphamide had to be given 2 days before busulphan. Improved survival was due to greater haemopoietic recovery in these animals compared with those that received busulphan alone. Details of these and subsequent experiments with these two drugs have been reported elsewhere [4]. It was further established that a pretreatment of 'priming' dose of cyclophosphamide did not protect the stem cells of the marrow from the cytotoxic effect of busulphan [5] or gamma radiation [6]. After bone marrow damage by busulphan or radiation there is normally a very protracted marrow stem cell recovery period, sometimes referred to as the 'post-treatment lag phase', and agents which successfully 'prime' the marrow operate by removing this lag phase and so accelerate the onset of the recovery of the haemopoietic system [7].

More recently these studies have been extended to show that a wide variety of cytotoxic agents, when used at appropriate low doses, will protect against radiation or drug-induced marrow lethality. These agents include cyclophosphamide, cytosine arabinoside, methotrexate and chlorambucil [7].

The bone marrow is not the only normal tissue that can be spared by drug pretreatment. Studies involving the administration of high-dose cyclophosphamide showed that pretreatment with low-dose cyclophosphamide 4 days before high-dose cyclophosphamide reduced the damage caused by the high-dose cyclophosphamide to the urothelium and improved animal survival [5]. Further, toxicity to mouse intestinal epithelium caused by the administration of high-dose melphalan could be reduced by pretreatment 2 days before with low-dose cyclophosphamide, cytosine arabinoside or melphalan itself [8]. Radiation given at high enough doses also critically damages the mouse intestinal epithelium and it has been shown that cytosine arabinoside given 12 hr before irradiation reduces the damage to this tissue [9].

During the course of these investigations the effect of normal tissue-sparing combinations of drugs has been tested against mouse tumours, initially the Lewis lung carcinoma [5, 8, 10] and the mouse fibrosarcoma FS6 [11]. In these preliminary studies it could be established that drug combinations which enhance the recovery of the normal tissues of the mice do not protect the tumour tissue.

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More recently these studies have been extended to include human tumours grown as xenografts in immune-deprived mice [12-14]. In none of these experiments did combinations protecting the normal tissues protect the tumour; thus a gain in the therapeutic index was achieved.

The mechanism of priming has not yet been elucidated. In early work [4] serum from mice treated with a priming dose of cyclophosphamide could rescue other mice heavily treated with busulphan when the serum was administered to the busulphan mice. This suggested that a passive, transferable factor was involved in the phenomenon. Alternately it has been suggested that in the case of radiation challenge, the pretreatment dose triggers the stem cells of the marrow into a less radiosensitive portion of the cell cycle, so providing a degree of protection [10]. Whatever the final explanation, it seems that tumours do not benefit from a pretreatment dose of cytotoxic agent and this might provide an exploitable difference between normal and malignant tissue. Attempts have been made to translate this phenomenon from laboratory to clinic. This involved investigating first whether normal tissue sparing could be detected in large mammals. Sheep were given a priming dose of cyclophosphamide and at variable times thereafter a large dose of melphalan. The results [15] indicated that an interval of 7 days between pretreatment and challenge was optimal for sparing the intestinal epithelium as assessed by histological examination. With this information members of this department began a study of the treatment of malignant melanoma in man in which patients were pretreated with cyclophosphamide and then given a large dose of melphalan a week later. Although the study was designed to protect the intestinal epithelium an early observation made on the first ten patients indicated that the bone marrow and subsequently the peripheral blood elements recovered more rapidly in pretreated patients than in patients who received melphalan alone [16]. More recently, using chromium labelled EDTA, it has been established that priming of the intestinal epithelium is not apparent at doses of melphalan less than 220 mg/m^2. Above these doses it appears that priming is beneficial to this tissue [McElwain and Selby, unpublished observation].

Recently a randomised trial has been conducted of cyclophosphamide priming before short-duration chemotherapy for small cell lung carcinoma [17]. In these studies there was no significant difference between the response rates and survival of primed vs unprimed patients, although survival of the primed patients was slightly better over the first 18 months post-treatment. The recovery of peripheral granulocytes after cyclophosphamide is rapid [18] and priming did not improve this recovery. Certainly the primed patients did not experience greater toxicities than the unprimed patients.

In conclusion, the priming phenomenon is a reproducible, easily demonstrable phenomenon in laboratory animals with evidence of therapeutic gain in tumour-bearing animals. It is less demonstrable in the clinic. This is probably because the agents and the timing of administration of the agents differs from small rodents to man and the appropriate experiments are difficult to do in man for ethical reasons. It is likely, therefore, that the underlying mechanism(s) of this phenomenon will have to be elucidated before any significant contribution from this observation can be brought to the clinic.

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