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Comments and Critique

Vascular Damage and Tumour Response

IT IS generally assumed that the primary mechanism by which chemotherapy brings about tumour regression is the direct killing of tumour cells; indeed, the first step in the search for new agents is invariably based upon their toxicity towards tumour cells grown in isolation. Yet there is increasing evidence that indirect mechanisms, including stromal and vascular damage, as well as activation of immune effector cells, may very effectively bring about tumour cell death. A recent paper in this journal [1] presented evidence for an important vascular-mediated component in the anti-tumour action of vinblastine, a "conventional" agent in wide-spread clinical use. The authors pointed out the similarities between the effects of vinblastine and those of the cytokine tumour necrosis factor (TNF)α, and concluded that, like TNFα, vinblastine acts on solid tumours by a host cell-mediated mechanism which induces vascular damage and loss of blood flow within the tumour. But just how this vascular damage is related to the ensuing tumour necrosis is unclear, and the subject of intense speculation. Does the loss of nutritional blood flow *per se* constitute a significant component of the effect of agents such as vinblastine, or is the mechanism more complex?

The supply of essential nutrients to a solid tumour may be compromised, either intentionally or spontaneously, in a number of ways, e.g. changes in systemic blood pressure may cause vessels to collapse due to perturbation of the delicate balance of hydrostatic forces pre-existing within the tumour [2]. Alternatively, vessels may be physically occluded by thrombi formed through the action of effector molecules which increase the procoagulant activity of the tumour-associated endothelial cells, as has been hypothesised for TNFα [3]. To examine the relationship between vascular insufficiency and tumour growth, Denekamp *et al.* [4] used mechanical clamps to produce total occlusion of blood flow to subcutaneously implanted murine tumours, and showed that clamping for a minimum of 15 h results in a significant number of tumour cures. These data imply that the intentional inhibition of blood flow to a solid tumour could play a therapeutic role; however, it is clearly not feasible in most clinical situations to deprive solid tumours of their supporting nutrients by the application of a clamp. While the pharmacological route might seem the more realistic option, the evidence to date supporting such an approach is not encouraging. During a study of the effects of combining the radiosensitiser misonidazole with melphalan on vascular function in murine tumours [5], we were surprised to observe that misonidazole alone caused a profound drop in blood flow specifically within the tumour, which persisted for at least 24 h; yet no effect on tumour growth was observed. In a similar manner, the vasodilator hydralazine produces a major reduction in blood flow in murine tumours [6], and potentiates the cytotoxic effects of melphalan [7], but again has no effect on tumour growth. Therefore, we might reasonably conclude that, short of physical intervention to bring about total vascular occlusion, the use of pharmacological agents solely to reduce tumour blood flow is unlikely to have a significant therapeutic impact.

Recently, interest in anti-vascular approaches was sparked by the appearance of flavone acetic acid (FAA), an anti-cancer agent which, at least initially, appeared to fulfil many of the criteria required of an ideal anti-vascular agent: it is very active against solid transplantable murine tumours, shows little or no cytotoxicity *in vitro*, causes a rapid, transient drop in tumour blood flow, and has few side-effects [8]. The drop in blood flow is accompanied by rapid activation of the clotting system, and we suggested this might cause vascular occlusion within the tumour [9]; like TNFα, FAA induces procoagulant activity on endothelial cells *in vitro*. In combination, FAA and TNFα act synergistically to enhance procoagulant activity *in vitro* and inhibit tumour growth *in vivo* [10]. It seemed possible, therefore, that much of the tumour response to a single dose of FAA might be due to vascular occlusion, brought about by direct effects on tumour-associated endothelial cells. However, in a critical series of experiments Bibby *et al.* [11] demonstrated that the effects of FAA on the growth of two transplantable tumours are lost when they are grown in "nude" or thymectomised hosts, although vascular shutdown and haemorrhagic necrosis still occur. These investigators concluded that while the vascular effects of FAA may be necessary to achieve growth delay, they alone are not sufficient. Subsequently, it was demonstrated that the anti-tumour activity of FAA is critically dependent upon a specific subpopulation of lymphocytes [12].

While these data would appear to relegate vascular shutdown to the sideline, the mechanism of action of this fascinating agent is still far from clear; it now seems likely that the potent cytokine-inducing properties of FAA play an important role [13]. Nevertheless, we are still left with an intriguing question: what is the significance of the severe reduction in tumour blood flow which accompanies the administration of tumour necrotising agents like FAA and TNFα; is it a peripheral phenomenon or does it play a critical role? The answer may continue to elude us for some time, awaiting a better understanding of the biology of inflammatory processes.

Whatever part a "vascular component" may ultimately play in the response of solid tumours to anti-cancer agents such as FAA, it is clear that many agents already in use cause vascular damage. Recent surveys [14, 15] note the high incidence of vascular pathologies in patients treated with conventional chemotherapeutic agents; such changes may, in many cases, relate to toxic effects on the endothelium [16]. Not surprisingly, the endothelial cell is itself a target for conventional chemotherapeutic agents: most drugs achieve their highest levels at the blood/endothelial interface, and endothelial cells within tumours

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are known to proliferate more rapidly than in most normal tissues [17], making these cells inescapably targets for cell cycle-specific toxins. No agent is currently available which specifically recognises endothelial cells within tumours. Indeed, while the endothelial cell is increasingly recognised as a potential target for therapy, the likely consequences for the tumour of direct damage to its associated endothelial cells are still unknown and a matter of speculation. A toxin derived from group B staphylococcus has recenty been described which preferentially binds to "immature" endothelium (a characteristic frequently attributed to endothelial cells associated with tumours), and produces haemorrhagic necrosis in human tumour xenografts [18]. Further investigations with this agent should provide some interesting data.

The potential therapeutic benefit of damage to the vasculature and, more specifically, the endothelial cells of tumours by conventional chemotherapeutic agents seems, for the most part, to have been overlooked. Nevertheless, the perceived boundary separating those agents which kill tumour cells directly, and those, like FAA (and now vinblastine), which exploit subtle but powerful biological mechanisms involving a complex interplay of vascular damage and immune effector cells, is becoming blurred. Perhaps we should pause and re-examine the mechanisms of action of other "conventional" chemotherapeutic agents. By the very nature of the way in which chemotherapeutic agents are screened, we may be overlooking some interesting new candidates. A better understanding of the role of the vasculature in tumour response to systemic therapy might just be an added bonus.

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Dilemmas in the Development of Cytoxic Drug Analogues

THE PAPER by Herait and colleagues on the early clinical assessment of a new anthracycline analogue (pirarubicin) in this month's *European Journal of Cancer* (**28**, 1670–1676), highlights the issue of using historical data to establish the relative cost-benefit of new compounds. The authors argue that the randomised clinical trial is an inappropriate way of determining whether a new drug is less toxic at an equi-effective dose than a standard drug, largely because of the difficulty of recruiting adequate numbers of patients into phase III studies. They suggest that 'historical comparisons, though they are unable to replace randomised studies, may be relevant for an *early* evaluation of the drug and can lead to further decisions on the development of phase III studies'.

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