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Tumour Angiogenesis and Metastasis

GROWTH OF solid tumours beyond a few millimetres diameter in size depends on the induction of a functional microcirculation from surrounding host tissue [1]. Conversely the maintenance of tumours in a "prevascular" phase requires that the cellular population can be supported by the simple diffusion of nutrients [1]. This latter state, exemplified by *in situ* carcinomas, is usually associated with limited tumour growth and the absence of metastases [1].

Regulation of tumour neovascularisation is not now thought to depend on the release of a single diffusible factor, common to all neoplastic tissues, but rather on the balance of effects resulting from the elaboration of several angiogenic polypeptides by both tumour cells and infiltrating normal cells [2]. The extracellular matrix proteins of the tumour stroma also may contribute to the phenomenon by exerting a direct angiogenic effect, by sequestering angiogenic polypeptides and by providing favourable attachment substrates for infiltrating endothelial cells [3]. This view of angiogenesis, occurring as a consequence of complex cell and tissue interactions, is as consistent with the observation of variable vascular composition between individual tumours as is the former idea that such differences reflected variation in levels of production and expression of a single "tumour angiogenic factor".

Elsewhere in this issue, Bicknell and Harris (p. 781) review the factors regulating angiogenesis and propose that antiangiogenetic therapy may eventually provide a useful adjunct to more conventional therapy.

The permissive role of angiogenesis in progressive tumour growth has been illustrated by the fact that a variety of angiogenesis inhibitors, lacking cytocidal or cytotoxic effects *in vitro*, are able to cause significant inhibition of tumour growth *in vivo* [1]. Recent reports have served to highlight this association between tumour development and angiogenesis. Thus Bouck and colleagues [4] reported that the loss of a tumour suppressor gene was linked to the acquisition of angiogenic activity. Non-tumorigenic cells were shown to produce both angiogenic factors and a 140 kD inhibitor which blocked the activity of such factors; loss of the suppressor gene correlated with loss of this 140 kD inhibitor and the simultaneous expression of angiogenesis and tumorigenicity [4]. The subsequent demonstration that the inhibitor protein is immunologically and functionally indistinguishable from a fragment of thrombospondin [5] illustrates that not all adhesive glycoproteins facilitate neovascularisation. Additionally, in an elegant study utilising a transgenic mouse model where oncogene expression was targeted to the β cells of the pancreatic islets, Folkman and co-workers [6] showed that onset of angiogenic activity preceded tumour formation and correlated with the transition from hyperplasia to neoplasia.

The evidence for the regulatory role of angiogenesis in tumour growth therefore is strong, but what part does the phenomenon play in the process of cancer metastasis? It has been noted in melanomas, for example, that intensity of angiogenesis can predict the probability of metastasis [7, 8]. Now a report from Weidner *et al.* [9] indicates that the assessment of tumour angiogenesis in breast carcinoma may predict the occurrence of metastatic disease in axillary lymph-nodes or at distant sites. Using immunocytochemical staining for factor VIII to detect endothelial cells these authors counted the number of microvessels per microscopic field in samples obtained from 49 patients with invasive breast carcinoma and found a significant correlation between microvessel density and metastasis [9]. While the sample size, admittedly, was small, these authors suggested that the assessment of tumour angiogenesis may be used as an aid to identify patients with early breast carcinoma who will require aggressive therapy [9]. Perhaps such an assessment, which would be simple to perform, will complement newer prognostic indices of metastatic propensity in breast cancer, like the presence of the *neu* oncogene protein [10] or down-regulation of *nm*-23 gene expression [11], to predict accurately the biological behaviour of individual tumours. Certainly the mere provision of an increased vascular network is unlikely to be the sole explanation for metastasis in all tumours since tumour dissemination is known to be a multistep phenomenon [12]. Nonetheless the potentially significant observations of Weidner and colleagues [9] will provide the impetus for closer examination of the correlation between angiogenesis and metastasis in numerous clinical cases which promises to increase our understanding of both these important phenomena.

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Ovarian Cancer Treatment: Time for Some Hard Thinking

INTRODUCTION

THE RESULTS of several carefully designed studies of the treatment of epithelial ovarian cancer are now available. As a consequence, we can modify the treatment strategy for such patients. Until now, the treatment plan for patients with disease outside the pelvis or distant metastasis (FIGO stage III and IV) included extensive surgical cytoreduction followed by chemotherapy with one to four drugs, restaging by ultrasound and computed tomography and a second laparotomy to restage or to remove remaining tumour. When tumour was present additional treatment was started. During follow-up, repeated ultrasound and computed tomography were used to detect relapse. For most of the parts of the treatment plan, recent studies have highlighted new facts and it is time for some hard thinking about whether we should change the treatment policy. The role of surgery, the choice of cytotoxic treatment, follow-up and treatment of relapse are aspects that deserve attention.

SURGERY

The surgical removal of as much tumour as possible during the initial laparotomy has long been part of the standard treatment. Protocols to resolve the influence of primary cytoreduction on survival were doomed to failure because of poor accrual of patients. One of the reasons for the low enthusiasm for such protocols is that when the abdomen is open for diagnostic purposes, debulking to tumour remnants of less than 1–2 cm is feasible in most cases without complications. Data from the Netherlands Joint Study Group for Ovarian Cancer show that removal of tumour down to microscopic disease results in 5 and 10 year survival rates of 62% and 37%, respectively. However, in patients with tumour remnants of more than 5 cm, the corresponding rates are 13% and 9%. Similar data have been presented by others, and primary cytoreductive surgery has therefore been accepted as part of the treatment plan.

More controversial is the role of intervention surgery (removal of tumour as soon as chemotherapeutic reduction renders the tumour masses resectable). Intervention surgery is most likely worthwhile in patients who had a biopsy only at first surgery, but not in patients who underwent a serious attempt at cytoreduction [1]. A randomised study of the EORTC to resolve this question is underway and the results will need to be taken into account before the role of intervention surgery as part of standard treatment can be defined.

The case is different for second-look surgery (exploratory laparotomy to assess the cancer status of a patient who has completed chemotherapy and is clinically free of disease). There is no place for this type of surgery. For, as we know, the detection of tumour at second-look laparotomy will not lead to the start of treatment alternatives with survival benefit. Those who state that second-look surgery can be accepted as part of research protocols have to consider that it is ethically questionable to perform a surgical procedure for research purposes only.

CHEMOTHERAPY

Cytotoxic treatment is the cornerstone in the treatment of advanced disease. With the addition of cisplatin to an alkylating agent about 80% of the patients respond and experience relief of symptoms and prolonged progression-free survival. With cisplatin-based combinations, the overall 5 year survival rates have been improved from 18% to 32%, with 21% of the patients alive at 10 year follow-up [2]. These results have been the basis of accepting these combinations as the initial standard treatment.

Carboplatin is thought to be as effective as cisplatin, but less emetogenic, and almost not nephrotoxic or neurotoxic. But caution should be exercised about replacing cisplatin in combinations for ovarian cancer and accepting carboplatin-based treatment as a new standard [3]. Long-term data from comparative studies are lacking, and only a few studies have been reported in detail so far. A disadvantage of carboplatin is that it is myelotoxic, and when carboplatin and cisplatin are compared at equitoxic myelosuppressive dosages, cisplatin treatment gives significantly better overall survival [4].

The results of studies comparing carboplatin in optimal dosage with cisplatin are difficult to interpret because patients randomised to receive carboplatin are subsequently treated with cisplatin and *vice versa*. This crossover from one treatment to the other before resistant disease emerges influences outcome in terms of progression-free and overall survival. In addition, the progression-free survival in these studies is calculated from the date of first surgery to the date of first progression, irrespective of whether progression occurred during carboplatin treatment or during subsequent cisplatin treatment. Survival is also a result of the activity of both carboplatin and cisplatin. That crossover is indeed not rare is illustrated in a large Italian study [5]. All patients with residual disease at second-look laparotomy and those with stable disease after three courses were crossed over to the alternative treatment, accounting for almost 60 out of the 82 carboplatin patients.

In ovarian cancer a dose-response relation is likely, and adjusting the dosage of carboplatin or delaying treatment cycles to permit recovery of leucocytes and platelets may diminish the results. This may be the reason that two large studies comparing

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