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Liver Metastases: Can Our Understanding of Their Biology and Prognostic Value Contribute to a Strategy for Optimum Therapeutic Management?

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Breast cancer is most likely to recur in soft tissue, liver, lungs and bone. The development of visceral disease, in particular liver disease, carries a poorer prognosis than the development of soft tissue or bony disease. Traditionally, liver metastases were believed to respond more poorly to hormonal approaches than other metastatic sites; although many studies of hormonal agents document a response in liver metastases in at least a proportion of the patients treated. Chemotherapeutic agents are generally considered the first-line of approach for women who have developed liver metastases from breast cancer, however. No well designed randomised studies have yet been carried out to compare the effects of various chemotherapeutic approaches using response in liver as a specific outcome. Many practitioners believe, even if this belief is not well documented in studies, that anthracyclines are more likely to produce shrinkage of liver metastases than some of the more traditional regimens such as cyclophosphamide/methotrexate/5-fluorouracil. More recently, it has been suggested from phase II data that liver metastases may respond more rapidly and completely to some of the newer agents such as the taxoids. Even in the setting of very aggressive chemotherapy, however, liver metastases retain their poor prognosis. Both disease characteristics and systemic adjuvant therapy have been linked to the site of recurrence of disease and considerable research into the molecular mechanisms mediating the distribution of metastases has been carried out. Despite the poor prognosis for patients with liver metastases, many new avenues are currently being explored to better understand and control this situation and, perhaps, to lead to the development of new treatment strategies for patients with this disease. © **1997 Elsevier Science Ltd.**

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INTRODUCTION

LIVER METASTASES from breast cancer, and indeed from most malignancies, have long been known to indicate an ominous prognosis. In spite of this strong clinical impression, little is really understood of the basic scientific principles that define their biology.

Seven per cent of women with breast cancer will present, at initial diagnosis, with widespread metastatic disease. Furthermore, of those patients who are apparently surgically cured, 20–30% with negative axillary nodes will relapse with metastases, while 50–60% of those with positive axillary nodes will develop widespread disease [1]. The most common sites of recurrence are the soft tissues (including nodes and skin), lungs and pleura, liver and bone [2]. Less common sites include the peritoneal cavity, adrenal glands, ovaries, brain and thyroid [3]. Once it has become widespread, breast cancer is incurable and all further therapy is palliative in intent. Thus, important outcomes in the treatment of patients with metastatic breast cancer include not only survival time and tumour response but also the toxicity of therapy and the patient's overall quality of life.

SITES OF METASTASES

Certain disease characteristics appear to be linked to specific sites at which breast cancer metastases develop. One such important characteristic is the disease-free interval (DFI), i.e. the length of time from the initial diagnosis to the first appearance of metastases. In a retrospective analysis of women who developed metastatic breast cancer, the investigators found that patients who developed bone metastases had had a median DFI of 2.4 years, while the DFI in those who developed visceral metastases was only 1.1 years [2].

A link has also been reported between the site of relapse and the results of the initial histological investigation. For

example, Borst and Ingold [4] reported that infiltrating lobular carcinoma is more likely than infiltrating ductal carcinoma to metastasise to the peritoneum, adrenals, uterus, ovaries and pleura.

Visceral metastases, including liver metastases, have also been reported to be less likely to contain oestrogen receptor (ER) positive (+ve) tumour [5]. This would suggest that ER is associated with some differential metastatic behaviour that leads to the more common development of liver metastases in patients with ER-negative (−ve) tumours or to the more common spread of the ER−ve portion of the tumour to the liver. Metastatic sites are also related to age and/or menopausal status. In a retrospective review, Sherry and colleagues reported that patients with bone-only metastatic breast cancer were more likely to have ER+ve tumours but were also likely to be postmenopausal, or older, while patients with visceral metastases were more likely to have ER−ve disease and to be younger and/or premenopausal [6].

RESPONSE TO THERAPY IN DIFFERENT METASTATIC SITES

Goldhirsch and colleagues, from the International Breast Cancer Study Group (IBCSG; formerly the Ludwig Group), have suggested that systemic adjuvant therapy also has a differential effect on sites of relapse [7]. The investigators carried out a retrospective analysis of a series of randomised trials of adjuvant therapy involving 2108 patients treated with (A) cyclophosphamide, methotrexate and 5-fluorouracil (5FU) plus prednisone (CMFp), with or without tamoxifen, or (B) tamoxifen and prednisone; and 722 patients who underwent observation alone or who were treated with only one perioperative cycle of chemotherapy. Based on the long-term results of these studies, the patients treated with A or B were considered to have had 'more effective' therapy than the patients who underwent observation alone or who received one perioperative cycle of chemotherapy. When the patients were monitored for the site of first relapse, the incidence of recurrence in bone and visceral sites was the same: 18 versus 17% in bone; 17 versus 19% in viscera, for more (A and B) versus less effective (observation or perioperative) therapy, respectively. The more effective therapy (A and B) resulted in an 18% relapse rate in locoregional and soft tissue sites, compared with a 36% relapse rate in the same sites in women receiving the less effective treatment. These values were significantly different at 10 years of follow-up. Goldhirsch and colleagues thus suggested that 'effective adjuvant therapy' differentially affects the occurrence of soft tissue and nodal metastases but not of bone and liver metastases. One possible explanation for this is that bone and liver metastases are more likely to come from ER−ve tumour clones whereas soft tissue and node metastases are more likely to come from ER+ve clones, which are more likely to be affected by tamoxifen or tamoxifen and prednisone. According to these data, however, chemotherapy may also be less effective in preventing recurrence in viscera or bone than in soft tissue.

BIOLOGY OF METASTATIC SPREAD

The frequent spread of metastases from primary breast cancer, as well from many other primary sites, to the liver is not completely understood. For some primary tumours, metastasis to the liver is likely because the first capillary bed encountered by the circulating malignant cells is in the liver. For example, in patients with colorectal cancer, the liver is an anatomically and physiologically obvious site for metastases to occur. By contrast, the frequent occurrence of liver metastases from primary breast cancer, melanoma and lung cancer cannot be explained on the basis of anatomical considerations alone. This predilection for liver metastases is likely to be an example of organ tropism, in which some features of the tumour and/or the site attract this particular distribution of metastases.

The molecular mechanisms mediating the distribution of metastases in various organs have been the subject of study by a number of investigators [8, 9]. Several theoretical mechanisms have been proposed for organ tropism [10]. Some investigators believe that tumour cells disseminate equally to all organs but grow preferentially in certain organ sites. This preferential growth may be induced by local growth factors or hormones present in the target organ. For example, insulin-like growth factors are present in liver and lung and have been shown to be important growth and motility factors for breast cancer, lung cancer and rhabdomyosarcoma [11]. Second, circulating tumour cells may adhere preferentially to the endothelial luminal surface in the targeted organ only. For this to occur, special recognition signals must be present on the endothelial cells to determine the specificity of the organ [9]. Nicholson has identified endothelial surface antigens that probably mediate preferential adhesion of circulating tumour cells from breast cancer to the endothelium of particular organs, including the liver [8]. Last, circulating tumour cells may respond to soluble factors diffusing locally out of the target organs. Such factors could act in a chemotactic manner, attracting the tumour cells to extravasate. These factors could also cause the circulating tumour cells to aggregate and therefore embolise in the target organ [12]. For example, some investigators have recently shown that α 6 β 4 integrin may mediate tumour cell adhesion to hepatocytes by mediating their extravasation specifically in the liver and thereby may be associated with the development of liver metastases [13]. In addition to soluble growth factors, the extracellular matrix or basement membrane is a source of organ-derived growth-regulatory molecules [14]. Both the extracellular matrix and basement membranes contain tightly bound growth factors [15]. Also, molecules from the extracellular matrix may modulate cell growth and differentiation. For example, the maintenance of most mammary cells is dependent on lactogenic hormones and on the appropriate cellular matrix [16]; isolated matrix molecules such as laminen and heparin sulphate proteoglycan can regulate gene expression and growth of malignant cells [17]. Although metastatic cells respond differentially to extracellular matrix molecules, often there is no clear simple relationship between organ preference of metastases and growth response to isolated matrix molecules such as heparin sulphate. When metastatic cells are grown on an organ-derived matrix, however, they can show organ-related growth characteristics. For example, Doerr and colleagues discovered that the extracellular matrix extracted from various organs did not equivalently stimulate the growth of metastatic rat mammary cancer and human hepatoma cells. Only the highly metastatic cells were differentially stimulated by the organ matrix from the target organ to grow at clonal densities sufficient for metastasis formation. They found that the glycosaminoglycan fraction from target organs was the most active growth regulator [18]. Thus, it is likely that organ growth microenvironments are collectively determined by

cell-bound, matrix-bound and soluble growth-regulating molecules.

From simple clinical observation it is clear that different patients with the same primary tumour may have different patterns of metastatic spread. Although the findings described above suggest that it is the 'soil' that determines the sites of metastases in many cases, there are some data to suggest that this may be influenced by the type of tumour rather than by specific host factors. For example, some human cancer cells grown in culture can be separated and cloned into different lines, which, when cultured in xenograft models, will home preferentially to one or other organ for which they seem to have an affinity. The molecular mechanisms for this phenomenon remain poorly understood.

PROGNOSIS IN RELATION TO METASTATIC SITE

Once relapse of disease has occurred, subsequent survival is greatly influenced by the sites of first relapse. Patients who initially develop bone-only metastases have a median survival time of 24–28 months, while those who develop visceral metastases have a median survival time of only 12 or 13 months [6, 19]. Sherry and colleagues showed that in 86 patients with bone-only metastases, the median survival time was 48 months and the 5-year survival rate was 33% [6]. In comparison, the median survival time of patients with extra-skeletal metastases was 17 months and the 5-year survival rate was 13%. In this group of bone-only metastatic patients, the development of non-skeletal metastases was a sign of poor prognosis, with a subsequent median survival time of only 9 months. Perez and colleagues in a retrospective review of 510 patients treated for metastatic breast cancer, found that patients with bony disease had a median survival time of 28 months compared with 13 months for those with visceral disease, a statistically significant difference [19]. In addition, a prospective study by Chiedozi of 60 women treated with CMFp chemotherapy found that patients with visceral disease had a median survival time of 6 months and that tumours were present for a median of 6 months before the patient sought medical attention, while women with skeletal metastases had a median survival of 12 months, following a 12-month median history of tumour presence before seeking medical attention [20]. Similar findings have been reported by others [21, 22]. Having said that liver metastases generally indicate a poor prognosis, however, it is important to stress that prognosis is still variable within metastatic sites. In patients with bone-only disease, various studies report prognoses ranging from 8 to 97 months median survival, while patients with visceral disease may have a prognosis varying from 1 to 14 months median survival [6, 19, 21, 22].

RESPONSE TO THERAPY IN VARIOUS METASTATIC SITES

Interestingly, the presence of liver metastases is also predictive of a reduced chance of response to chemotherapy [23–26]. Nash and colleagues [23] used univariate and multivariate regression methods to analyse 17 potential clinical prognostic factors among 138 patients with advanced breast cancer receiving doxorubicin-cyclophosphamide (AC) combination chemotherapy between 1973 and 1977 at the University of Arizona. The six most important prognostic factors predicting an objective response to chemotherapy were age (older patients being more likely to respond, $P=0.006$), treatment (patients treated with higher dose AC being more likely to respond, $P=0.007$); liver involvement (patients without liver involvement being more likely to respond, $P=0.033$); number of sites (patients with fewer sites being more likely to respond, $P=0.065$); performance status ($P=0.12$) and soft tissue involvement (patients with soft tissue involvement being more likely to respond, $P=0.18$). A study from the University of Texas M.D. Anderson Cancer Center in 619 women with metastatic breast cancer treated with 5-fluorouracil (5-FU), doxorubicin and cyclophosphamide chemotherapy showed that a group of variables including carcinoembryonic antigen concentration, alkaline phosphatase concentration and α glutamyltranspeptase concentration provided a serum marker profile that was generally reflective of liver metastases and predictive of a lower response to chemotherapy [24].

Similarly, investigators from the South East Oncology Group (SEG) and from the South West Oncology Group (SWOG) found the presence of visceral metastases and/or of liver metastases to be predictive of poorer response to chemotherapy. In the SEG study of 304 patients treated with cyclophosphamide, methotrexate, 5-FU, vincristine and prednisone (CMFVP), the absence of visceral metastases and the presence of a higher performance status were both predictive of a higher response rate to chemotherapy [25]. In the SWOG analysis, 281 patients treated with doxorubicin or CMFVP showed a higher response to either chemotherapy in women with a longer DFI, a higher performance status and/or the absence of liver involvement [26]. In general, the presence of liver metastases affects both the chance of response to chemotherapy and the patient's overall prognosis, perhaps in part due to its predictive value for poorer response.

Similarly, it is generally accepted that soft tissue and bony lesions respond better to hormone therapy than do visceral metastases, perhaps in part because visceral metastases are less likely to contain ER+ve tumour [5, 27]. Response rates to hormone therapy have been shown to vary greatly with the site of metastases, being up to 70% in bone and perhaps only about 20% in visceral metastases [27–30]. Parnes and colleagues for example, reported a 33% response rate to megestrol acetate in patients with soft tissue sites of disease, a 70% response or stabilisation with bony disease and only a 21% response rate in patients with visceral sites of disease [31]. Similar data have been reported by others [32, 33]. Once again, because many of the factors related to the presence of liver metastases (lack of ER, short DFI, etc.) are also linked to a poorer response, it is unclear which factors, if any, are directly responsible for the poorer response. It seems clear, however, that liver metastases, regardless of the mechanisms by which they do so, respond more poorly both to chemotherapy and to hormonal agents.

Many clinicians have the impression that anthracyclines are more effective against liver metastases than older antineoplastic agents, but this is poorly documented in the literature as shown above. There have also been suggestions that the newer agents, particularly the taxoids, may be more effective against liver secondaries. These data are reviewed in detail by Fumoleau [34]. There are, however, increasing data showing that even with very high-dose or intensive therapy supported by stem cell transplant, liver secondaries may still carry a poor prognosis [35–37].

SUMMARY

In conclusion, although liver metastases retain a poor prognosis for the patient because of the life-threatening nature of the location, their association with apparently aggressive breast cancers and their poor response to hormonal therapy, standard chemotherapy and even dose-intensive chemotherapy, many new avenues are being explored to better understand and control these metastatic tumours. Perhaps with more detailed understanding of the biological factors underlying the development of liver metastases, drugs can be developed that might specifically reduce the growth of liver metastases or prevent their establishment, if given in the adjuvant setting. Clearly, a better understanding of the biology of these phenomena has tremendous potential to lead to more specific and, therefore, more effective and less toxic therapies for this disease. In the meantime, the promise shown by some of the newer chemotherapeutic agents, which may be more active for breast cancer in general and against liver metastases in particular, is of considerable interest. We will await with anticipation the results from ongoing and future trials in this area.

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