Bone Marrow Carcinosis and Disseminated Tumour Cells

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The occurrence of overwhelming bone marrow infiltration by solid tumour cells is rarely reported. Despite the paucity of published data, this is not rare clinically and is often seen as a late-stage event. The article by Flörcken and colleagues in the October 2009 issue of ONKOLOGIE is indeed relevant [1]. The authors state that where bone marrow carcinosis has been reported it is usually associated with a large burden of disease, rapid progression and death. Yet there have been positive reports of long-term disease control in bone marrow carcinosis caused by solid tumours [2, 3]. The 63-year old female patient described by Flörcken and colleagues died within 5 months of initial presentation [1]. The diagnosis of metastatic renal cell cancer was confirmed after investigation of thrombocytopenia. This is an unusual complication of renal cell cancer and to our knowledge the first reported case.

Unexplained or progressive cytopenias in cancer patients should raise the possibility of bone marrow carcinosis. For patients without a cancer diagnosis, though other causes of bone marrow failure should be investigated, early bone marrow biopsy may help to diagnose the primary site of malignancy. Nuclear medicine bone scan and bone marrow biopsy are required to establish the diagnosis of disseminated carcinomatosis of the marrow. Bone scintigraphy commonly demonstrates a super-scan of malignancy. Bone marrow trephine generally exhibits the highest yield for detecting metastatic disease, as aspiration may prove unsuccessful due to fibrosis [4]. The marrow serves as a reservoir of tumour cells with the potential to metastasise. The physical burden of tumour cells within the bone marrow may eventually interfere with haematopoiesis, haemostasis and immune responses. Bone marrow carcinosis then becomes clinically significant, often compounded by myelosuppressive cytotoxics.

The incidence of bone marrow carcinosis was investigated in 380 breast cancer patients at the time of first recurrence. 87 patients (23%) had sufficient tumour cells in the bone marrow

to be deemed bone marrow carcinosis. Matrix bone metastases were demonstrated in 78% of patients with bone marrow carcinosis versus only 16% of the patients without bone marrow carcinosis. Heavy tumour infiltration of the bone marrow was associated with multiple bone lesions with histopathologic evidence of bone destruction [5]. This study provided evidence that the primary soil of metastatic bone disease in breast cancer is the bone marrow. Bone metastases are the result of invasion and destruction of bone tissue matrix mostly by tumour cells from within the marrow cavity.

Intuitively, if bone marrow carcinosis heralds progression, the presence of even a small number of metastatic cells within the bone marrow should correlate with poor outcome. Disseminated carcinoma cells (DTCs) are clearly detectable in the bone marrow very early in the diagnosis of many solid tumours [6]. DTCs are distinct from frank bone marrow carcinosis as they are not associated with marrow dysfunction. However, clearly both exist on a continuum. Cells appear to disseminate from early primary lesions and then acquire additional genetic defects. Gene expression patterns of DTCs are often strikingly similar to the cells from the primary tumour [6]. The bone marrow may form the preferred reservoir for metastatic tumour cells, from where they re-circulate to distant organs where better growth conditions exist. The presence of DTCs in the bone marrow of primary breast cancer patients is an independent prognostic indicator of relapse, correlating with the appearance of bone metastases and with the occurrence of overt metastasis at other sites [7]. Significant correlations have been shown between DTCs in the bone marrow and metastatic relapse [8].

Animal models indicate that a significant proportion of DTCs remain dormant or perish, never developing into overt metastases [9]. Dormancy can be defined as slow-growing tumours that appear after long latency periods, quiescent tumours with no growth at all, or tumours that are in prolifera-

tive and apoptotic equilibrium. Cancer dormancy represents a potentially useful therapeutic goal [10]. An intriguing issue related to the apparent dormant, non-proliferating nature of many DTCs is the trigger that initiates proliferation. HER2 appears to define an aggressive subset of DTCs associated with poor prognosis in breast cancer [11] and expression of urokinase-type plasminogen activator receptor (uPAR) has been correlated to metastatic relapse in gastric cancer [12], suggesting that signalling mediated by HER2 and uPAR might be important for the transition of DTCs from a dormant stage to an active growth phase [13]. In addition adaptive immunity has been observed to play an important role in dormancy [14]. Tumour equilibrium constitutes part of what can be described as the 'immuno-editing' process. In mouse models of dormant tumours (equilibrium between cell growth and cell death) depletion of CD4 and CD8 cells, combined with inhibition of interferon- γ , initiated progressive growth [14].

Despite their strong prognostic significance, DTCs or CTCs (circulating tumour cells in the peripheral blood) will only have a convincing clinical application if they can be reliably measured and are proven to be a surrogate marker for treatment efficacy. To date the ASCO recommendations are that detection of DTCs, and CTCs have yet to demonstrate sufficient evidence to support routine use in clinical practice [15].

The presence of malignant tumour cells within the bone marrow offers both challenges and opportunities to clinicians. There is growing evidence that bisphosphonates, used as standard treatment for proven bone metastases to reduce skeletal events, can impact on the development of distant non-osseous visceral disease [16]. Murine models have demonstrated that treatment with zoledronic acid resulted in a reduction in the number of bone, liver and lung metastases and increased overall survival [17]. In contradiction to the conventional theory that metastatic invasive tumour cell dissemination is a late event, animal models have indicated that premalignant lesions can disseminate early and may even become evident as metastases before an invasive primary has become apparent [18]. It is postulated that bisphosphonates lead to the creation of an unfavourable bone marrow stromal 'soil' whereby dormant DTCs are eradicated interrupting their development into measurable clinical disease. Such concepts

have been used to support the trials of adjuvant bisphosphonates with conventional treatment in early solid tumours.

The Austrian Breast and Colorectal Cancer Study Group ABCSG-12 trial [19] is the first clinical study to report an improvement in long-term outcome in early-stage cancer by the addition of a bisphosphonate. Over 1,800 premenopausal women with stage I/II breast cancer were treated by biochemical ovarian suppression with an initial randomisation to tamoxifen or an aromatase inhibitor, followed by a subsequent randomisation to zoledronic acid every 6 months for 3 years or no additional therapy. The addition of zoledronic acid resulted in a significant reduction in the risk of a DFS event (hazard ratio 0.64; 95%CI 0.46–0.91 $P = 0.01$). Zoledronic acid seemed to reduce all categories of DFS events including distant non-osseous relapses, locoregional recurrences and contralateral primary breast cancers. In addition preliminary data from the neoadjuvant run-in portion of the AZURE (Adjuvant Zoledronic Acid reduce Recurrence) trial has shown a higher rate of pathological complete response compared to chemotherapy alone but long term survival and distant metastasis data are keenly awaited [20].

In this era of targeted oncological therapy, cytotoxic chemotherapy is no longer the only available treatment option. For advanced bone marrow carcinosis rapid disease control is required and this may be best achieved with chemotherapy and bisphosphonates with or without targeted agents. This obviously will depend on the chemosensitivity of the disease and dosing will be dependent on the degree of marrow dysfunction. Most clinical trials do not routinely exclude patients on the basis of bone marrow carcinosis, however the requirement of 'adequate' bone marrow function prior to therapy excludes many such patients. It would be unrealistic to consider designing a clinical trial specifically to address the best treatment modality for bone marrow carcinosis, so data will remain scarce. However case series and case reports such as this one will continue to increase our knowledge of this important area.

Conflict of Interest

Dr. Kelleher and Dr. Kendall have no disclosures; Dr. Chowdhury is a member of advisory boards for Novartis, Sanofi and GSK.

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