Chapter 3

DETECTION AND CHARACTERISATION OF OCCULT METASTATIC CELLS IN BONE MARROW OF BREAST CANCER PATIENTS: IMPLICATIONS FOR ADJUVANT THERAPY

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Abstract

The early and clinically occult spread of viable tumour cells to the organism is becoming acknowledged as a hallmark in cancer progression, since abundant clinical and experimental data suggest that these cells are precursors of subsequent distant relapse. Prospective clinical studies have shown that the presence of such immunostained cells in bone marrow is prognostically relevant with regard to relapse-free and overall survival of breast cancer patients. As current treatment strategies have not resulted in a substantial improvement of breast cancer mortality rates so far, it is noteworthy to consider the intriguing options of immunocytochemical screening of bone marrow aspirates for occult metastatic cells. Besides improved tumour staging, such screening offers opportunities for guiding patient stratification for adjuvant therapy trials, monitoring response to adjuvant therapies, which, at present, can only be assessed retrospectively after an extended period of clinical follow-up, or for specifically targeting tumour-biological therapies against disseminated tumour cells.

1. INTRODUCTION

Occult dissemination of tumour cells in patients with operable breast cancer may be a crucial step in carcinogenesis and subsequent metastasis formation, yet conventional tumour staging usually does not reveal it. To identify individual tumour cells that have successfully escaped from the primary tumour and invaded secondary organs several research groups established sensitive immunocytochemical and molecular assays (1). Because of its easy accessibility and physiological absence of epithelial cells, bone marrow plays a prominent role as determinant for micrometastatic organ involvement (2–4). In breast cancer, bone also represents a relevant site of distant metastasis suggesting that bone marrow is a relevant site

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for the search of early dissemination of metastatic cells. In consequence, the development of antibodies to epithelial differentiation antigens, such as cytokeratins, as major constituents of the epithelial cytoskeleton, and tumour-associated cell membrane glycoproteins, enabled diagnosis of disseminated tumour cells as early as at primary diagnosis (2, 5).

Compared to the well-documented prognostic significance of isolated tumour cells disseminated to bone marrow, their biological characteristics remain poorly understood. This lack of knowledge requires an explanation, particularly for patients with micrometastatic bone marrow involvement who have not developed manifest (bone) metastasis during observation after surgery. It is therefore conceivable that differential biological properties of disseminated tumour cells in bone marrow exist. Individual characteristics of the respective tumour cells influence their differential homing and outgrowth of metastases. Thus, disseminated tumour cells may not necessarily have the potential to form clinically detectable metastases in this particular environment, but may rather remain dormant for years. Support for the concept of dormancy is also derived from the clinical observation that distant metastases can manifest themselves as late as 10 years after the excision of a primary tumour (6).

The emerging data supporting the prognostic relevance of this phenomenon (7) point out that appropriate therapeutic approaches directed against dormant micrometastatic cancer cells need to be evolved urgently. It is known from the clinical practice that both loco-regional and distant tumour recurrences occurred in patients treated with curative intent, e.g., complete tumour resection (R0) in patients without lymph node (N0) and distant metastases (M0). This is also true in cases where systemic cytotoxic chemotherapy was applied, which pointed to the existence of at least some resistant tumour cells. Although various mechanisms may contribute to this apparent chemo-resistance, the latter assumption could be supported by the absence of proliferation-associated markers on disseminated tumour cells in bone marrow (8). In this view cell cycle independent treatment strategies, such as antibody-based immunotherapy, which have been recently shown to be active in breast cancer (9, 10), might gain increased interest for the design of future clinical trials. The present review focuses on the prognostic relevance and characterisation of occult metastatic cells in bone marrow of breast cancer patients and the implications of this knowledge for adjuvant therapy.

2. PROGNOSTIC RELEVANCE OF OCCULT METASTATIC CELLS

Before elucidating the implications of occult metastatic cells for systemic cancer treatment, it needs to be clarified how the presence of such cells contributes to a clinically relevant stratification for specific therapy. From a clinical point of view, it also needs to be discussed which of the investigated body compartments – including bone marrow (BM), peripheral blood (PB), and lymph nodes (LN) – provide the most reliable prognostic estimation.