Chapter 4

PROGNOSIS OF MINIMAL RESIDUAL DISEASE IN BONE MARROW, BLOOD AND LYMPH NODES IN BREAST CANCER

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Abstract

The most important factor affecting the outcome of patients with invasive cancers is whether the tumor has spread, either regionally (to regional lymph nodes) or systemically (to the bone marrow). However, a proportion of patients with no evidence of systemic dissemination will develop recurrent disease after primary therapy. Clearly, these patients had occult systemic spread of disease that was undetectable by methods routinely employed (careful pathological, clinical, biochemical and radiological evaluation). This early dissemination of tumor cells is known as occult metastases (or micrometastases). In addition, the success of adjuvant therapy is assumed to stem from its ability to eradicate occult metastases before they become clinically evident. Therefore, methods for the detection of occult metastases in patients with the earliest stage of cancer, i.e., prior to detection of metastases by any other clinical or pathological analysis, have received a great deal of attention. This chapter focuses on the detection and significance of occult metastatic cells in the peripheral blood bone marrow and lymph nodes of patients with breast cancer.

1. OCCULT METASTASIS

The goal of diagnostic surgical pathology is twofold: to arrive at the specific diagnosis (benign or malignant and cell of origin) and to stage the tumor (1). These are the two important parameters that determine the rational treatment of any type of tumor. Using pathological criteria in conjunction with clinical parameters, the pathologist and the clinician attempt to determine the outcome of a patient. Staging criteria are used to evaluate almost any type of solid tumor and are important not only in predicting prognosis, but also in selecting appropriate therapy.

The majority of patients with newly diagnosed breast cancer have operable disease, and these patients are considered potentially curable. However, 35% to 40% of these patients, including up to 24% of patients with no evidence of metastasis at the time of diagnosis, develop recurrent disease after primary

K. Pantel (ed.), Micrometastasis, 67–85.

therapy. The most reliable prognostic parameters (lymph node status and tumor size) cannot predict which particular individual will progress. As a result, several groups have recommended adjuvant treatment for patients with lymph node negative disease. While this is controversial (since the majority of node negative patients will be clinically cured without adjuvant therapy), it is in this group of patients who have minimal occult metastases that adjuvant therapy should be most successful. It would be of great value, therefore, to be able to further discriminate and identify those patients with early-stage disease who are most likely to recur. Detection of occult metastatic cells in these patients could be extremely beneficial in determining prognosis and in making treatment decisions.

1.1 Methods Used for the Detection of Occult Metastases

Several techniques have been used to identify occult metastases. The most important of these include: immunohistochemistry (IHC), flow cytometry, and molecular methods, usually the reverse-transcriptase polymerase chain reaction (RT-PCR) technique. These different methodologies vary in their ability to identify occult metastases, and as well as in their ability to predict outcome. The pros and cons of these techniques are discussed below.

1.1.1 Immunohistochemistry

Following pioneering studies at the Ludwig Institute and Royal Marsden Hospital in London, England (2), a number of groups have used immunohistochemical procedures to identify occult metastatic cancer cells in the peripheral blood bone marrow of patients with cancer. While many of the initial studies focused on breast cancer (2–6), tumors from other organs, such as colon (7–9), prostate (10–13) and lung (14–18), have also been investigated. Immunohistochemical methods are based on the ability of monoclonal antibodies to distinguish between cells of different histogenesis (i.e., epithelial cancer cells vs. hematopoietic cells, and cells of the peripheral blood, bone marrow and lymph nodes (Figures 1 and 2)). The results indicate that it is possible to identify occult metastatic cancer cells in these compartments prior to their detection by routine histologic analyses, and that the presence of these cells may be an important risk factor for disease recurrence.

The most widely used monoclonal antibodies to detect occult metastatic cells are antibodies to epithelial-specific antigens. These antibodies do not react with hematopoietic cells normally present in the peripheral blood, bone marrow and lymph nodes. None of the antibodies used in any study is specific for cancer; all react with normal and malignant epithelial cells. They are useful because they can identify an extrinsic population of epithelial cells in the blood and bone marrow, where there are normally no epithelial elements. The reported sensitivity of the immunohistochemical method ranges from the detection of one epithelial cell in 10,000 (3) to that of two to five epithelial cells in a million hematopoietic cells (3, 6).