Breast Cancer: Understanding Sensitivity and Resistance to Chemotherapy and Targeted Therapies to Aid in Personalised Medicine

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Abstract: Breast cancer is the second leading cause of cancer deaths. This disease is estimated to be diagnosed in over one million people worldwide and to cause more than 400,000 deaths each year. This is a significant health problem in terms of both morbidity and mortality. Chemotherapy forms part of a successful treatment regime in many cases; however, as few as half of the patients treated may benefit from this, as a result of intrinsic or acquired multiple drug resistance (MDR). A range of mechanisms of MDR has been identified using *in vitro* cell culture models; many, if not all, of which may contribute to breast cancer resistance in the clinical setting. This phenomenon is complicated by the heterogenous nature of breast cancer and the likely multi-factorial nature of clinical resistance. It has been very well established that a "one treatment fits all" approach is not relevant and significant advances have been made through identifying and appropriately treating sub-groups of patients; particularly with newer rationally-targeted therapies, such as the HER2-targeted monoclonal antibody, Trastuzumab, and the dual HER2 and EGFR tyrosine kinase inhibitor, Lapatinab. Furthermore, large defined collaborative studies, using standardised global profiling approaches to study mRNA, microRNAs and proteins, followed by functional genomics studies, by ourselves and others, are underway in order to definitively establish the degree of complexity contributing to drug resistance. The overall vision is to identify the optimum therapeutic regime for individual patients -possibly involving novel targeted therapies, drug resistance modulators, and chemotherapy- to overcome breast cancer.

Keywords: Breast cancer, biomarkers, chemotherapy, targeted therapy, multiple drug resistance, molecular profiling, cancer stem cells, circulating tumour cells, extracellular mRNA, extracellular miRNAs, exosomes.

INTRODUCTION

Breast cancer is the most common cancer in women, excluding non-melanoma skin cancers. Breast cancer is not restricted to the female population; approximately 1% of all breast cancer cases are diagnosed in men. This disease directly affects approximately 12% women at some stage during their life-time [1]. According to the American Cancer Society, the probability of developing breast cancer within the next 10 years of the age of 20 years is 1/1985; of the age of 30 years is 1/229; of the age of 40 years is 1/68; of the age of 50 years is 1/37; of the age of 60 years is 1/26; and of the age of 70 years is 1/24. The 5 year survival rate when diagnosed before the age of 45 years is 81%; between 45-64 years, is 85%; and 65 years and older of 86%. The median age for breast cancer is 65 years [2, 3]. Although breast cancer is less common at a young age (*i.e.* in the thirties), younger women tend to have more aggressive breast cancers and a higher incidence of basal-like tumours than older women. This may explain why survival rates are lower among younger women (http://www.imaginis.com/breast-health/statistics_print.asp?mode=1). Fortunately, due to earlier detection and better treatments, breast cancer death rates have been dropping steadily since 1990. Still, however, approximately 1.3 million women are diagnosed with breast cancer annually worldwide and approximately 465,000 die from the disease. Whereas in the US more than 90% of breast cancer diagnoses now occur during the early stage of this disease [4], in developing countries approximately 25-30% of cases have already advanced locally when first diagnosed [1].

The most common type of breast cancer is ductal carcinoma, which is invasive. Ductal carcinoma, as the name suggests, starts in the milk ducts, but has developed the potential to spread to other parts of the body. Lobular carcinoma, which originates in the milk-producing lobules, is also invasive. Inflammatory breast cancer, a rare type of advanced cancer, has poorest prognosis; it results from lymphatic vessels becoming blocked with tumour cells and then becoming inflamed. Other forms of breast cancer include Paget's disease, comedocarcinoma, medullary carcinoma and colloidal carcinoma [5]. Although histology may influence treatment decisions, the stage of disease is usually considered to be more important. Poorly differentiated (high grade) tumours have a worse prognosis than well-differentiated (low grade) tumours. Inflammatory carcinoma has a poor prognosis, irrespective of stage. For patients with negative nodes, a group of "special tumour types" (typical medullary, mucinous, papillary, and pure tubular types) is associated with a better prognosis. For early disease without lymph node involvement (stage I), the 5 year survival rate is approximately 80% for invasive ductal carcinomas and 90-95% for invasive lobular, comedocarcinomas, and colloid carcinomas. Unfortunately, breast cancer cells often detach from the primary tumour site and, in the form of circulating tumour cells (CTCs) (see *Circulating Tumour Cells* later), metastasise to secondary organs *via* lymph and blood vessels. The most common organs affected by symptomatic metastases are regional lymph nodes, skin, bone, liver, lung and brain. In fact, axillary lymph node metastases are reported to be present in 55-70% of patients at the time of diagnosis when not detected by screening mammography [5].

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