The Evolution of Breast Tumor Therapeutics – A review

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Survival rate among breast cancer patients has significantly increased over the past 20 years due to improved therapeutic regimens and better screening strategies. Though the mainstay of tumor treatment has been surgical removal of the tumor mass, it is the improvement in adjuvant chemotherapeutic armamentarium that has contributed most to a decline in the death rate. With an increase in knowledge about the biology of breast cancer, treatment regimens have evolved from the use of non-specific drugs that target the bulk of proliferating cells (like paclitaxel and cyclophosphamide), to drugs that selectively target specific hormonal pathways (tamoxifen) and monoclonal antibodies targeting particular growth factor receptors (such as trastuzumab). This review describes the chronological advancement in our understanding of the disease and discusses how that knowledge-base was translated to more effective therapies.

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Introduction

BREAST CANCER is the most commonly diagnosed cancer among North American women and is the second leading cause of death, next only to lung cancer. In 2008, an estimated 22,600 Canadians will be diagnosed with the disease and 5,400 are likely to die from it (1). Current estimates suggest that one in nine Canadian women will develop a breast tumor in her lifetime. Despite these large numbers, the death rate among breast cancer patients has declined by more than 25% since 1986 and the incidence rate of developing a tumor has decreased by a significant 1.7% on average over the last decade (1). This remarkable feat is primarily attributable to three important factors: better diagnosis by mammographic screening, increased self-awareness among women leading to early diagnosis, and—perhaps the most effective of all—availability of better and more effective molecular therapies. Furthermore, the growing understanding of the basic biology of breast cancer and its impact on clinical management of the disease is defining new paradigms of tailoring treatments to particular tumor types.

Historical beginnings of breast-cancer chemotherapy

The principle of adjuvant chemotherapy for

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the treatment of solid tumors was established in 1974 when Jaffe *et al.* demonstrated that high doses of methotrexate with leucovorin prevented recurrence of osteosarcoma following surgical removal of the primary tumor (2). However, the era of adjuvant chemotherapeutic treatment of breast cancer dawned in 1976 with the landmark trials by Gianni Bonadonna which showed that combinatorial chemotherapy involving cyclophosphamide, methotrexate and 5-fluorouracil (CMF) significantly extended overall survival among women whose tumors were surgically removed (3). It also established CMF as the first chemotherapeutic regimen for the treatment of breast tumors.

The individual constituents of the CMF regimen belong to three different classes of chemical compounds: nitrogen mustard, antifolate and purine analogues. They act in concert through complimentary mechanisms that induce apoptosis in proliferating cells, reducing clinically-observed drug resistance with the use of single-agent treatments (4, 5). Since the integration of CMF into the clinical regimen of treatment for malignant breast cancer, several additional clinical trials (6-9) were undertaken to answer important questions about adjuvant chemotherapy including: What is the optimal combination of drugs? What are the most advantageous doses of the agents used for adjuvant chemotherapy? How long should they be administered? Does the inclusion of additional classes of anticancer drugs like anthracyclines, which intercalate into the DNA double helix structure and prevent replication, or taxanes, which inhibit microtubule assembly leading to mitotic arrest, improve the clinical outcome? A meta-analysis of several clinical trials addressing these questions ascertained some important facts. First, the finding that as compared with CMF, anthracycline-containing chemotherapy was associated with significant reductions in the rates of recurrence and death, led to the incorporation of anthracyclines (epirubicin, doxorubicin, daunorubicin) within the standard therapeutic regime. Second, the observation that incorporation of taxane (paclitaxel) into anthracycline-containing regimens in sequential therapy showed improved outcome as compared with anthracycline alone (10), and further increased the arsenal of available drugs for tumor treatment.

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The targeted-therapy revolution

Until the mid-1970s, combinatorial cytotoxic chemotherapy remained the mainstay of cancer treatment. Clinicians and industrial researchers were convinced that the right combination of cytotoxic agents applied at the right time was the key to cure cancer. Therefore, despite substantial evidence suggesting a link between hormone signaling and breast cancer (11-13), there was little interest among pharmaceutical companies to invest in developing new antihormone therapies.

Coincidentally, during this same period, researchers at the ICI pharmaceuticals (now AstraZeneca) reported antiestrogenic and antifertility properties of an investigational compound, ICI 46464 (tamoxifen) belonging to the chemical class of substituted triphenylethylene (14, 15). Though tamoxifen was a very effective antifertility agent in lab animals,

it showed no evidence of contraceptive properties in humans and had an almost opposite action of promoting ovulation in subfertile women. Thus, it failed in its intended purpose to be used as a morning-after contraceptive (16-18). This failure prompted the researchers to explore the antiestrogenic properties of tamoxifen for other probable applications. An investigation of its use for breast cancer treatment was one of the most obvious choices because of the strong evidence of hormonal signaling in initiation and maintenance of tumors. Laboratory experiments demonstrated that tamoxifen blocked the binding of estradiol to estrogen receptors (ER) in human breast and rat mammary tumor tissue and also prevented the induction and growth of ER positive dimethylbenzanthracene (DMBA)-induced rat mammary carcinomas (19-22). These studies together with pilot clinical trials (23, 24) provided the rationale for the long-term use of tamoxifen in clinic to treat early node-positive and node-negative, ER positive tumors. Overview analysis of several small randomized clinical trials conducted over the next 20 years (25-27) conclusively established tamoxifen as a 'gold standard' treatment for ER positive tumors.

Thus, the drug that was originally designed with an intended use as a postcoital contraceptive went on to be crowned as the first targeted therapy for advanced breast cancer. Further research unveiled the prophylactic properties of this molecule in animal models (28) and in high-risk patients (29). This led the United States Food and Drug Administration (USFDA) to approve the use of tamoxifen for the reduction of breast cancer risk in pre- and postmenopausal women in 1998.

The mechanism of action studies revealed that tamoxifen acted as a partial estrogen agonist/antagonist, depending on the site of action (15, 30, 31). This finding raised serious concerns about tamoxifen as an optimally effective chemotherapeutic agent against breast cancer, and outlined its possible adverse estrogenic effects. It led Angela Brodie and her colleagues to develop an alternative approach of modulating estrogen signaling by blocking its endogenous synthesis from androgens using compounds belonging to the class of 'aromatase inhibitors'. These act by suppressing the action of the aromatase enzyme complex, which catalyzes this conversion (32-34). These compounds act by competitively binding to the active site and subsequently inactivating the enzyme, rendering it incapable of acting

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on its natural androgen substrates (34, 35). In 1993, formestane, a steroidal aormatase inhibitor, became the first drug of this class to enter into clinical trials (36). It was directly compared with tamoxifen as a first-line treatment and was shown to have equivalent efficiency (36). Subsequently, other aromatase inhibitors including anastrozole (37), letrozole (38) and exemestane (39) entered the clinic and were shown to be more effective than tamoxifen in treatment of breast cancer in large, randomized, double blind, multicentre trials.

While Angela Brodie's group was busy with the

development of formestane that inhibits estrogen synthesis, scientists at Genentech, a start-up biotech firm, were pursuing another molecular target – HER2/*neu*. The human epidermal growth factor receptor 2 (HER2) is a member of the epidermal growth factor receptor (EGFR) family of transmembrane tyrosine kinases involved in signal transduction pathways that regulate cell growth, migration, differentiation and proliferation (40). Clinically, the relevance of HER2 as a potential therapeutic target was hinted when correlation studies by Slamon et al. convincingly linked the over-expression of HER2/*neu* with poor prognosis in invasive metastatic breast cancer patients (41). Further, transgenic murine studies showed that expression of *neu* in mammary epithelium was sufficient to induce metastatic mammary adenocarcinoma (42-44). It provided evidence of the causative involvement of HER2 overexpression in metastatic transformation which was missing in the clinical correlation studies. Together, these findings persuaded Genentech researchers to utilize an antagonistic approach to HER2 signaling as a novel therapeutic strategy. With this rationale, trastuzumab (herceptin)—a recombinant humanized monoclonal antibody that blocks the receptor tyrosine kinase HER2—was developed. In the clinical trials leading up to trastuzumab's approval, 42% of patients taking the drug in combination with paclitaxel displayed significant responses in comparison to 16% for paclitaxel alone (45). The drug was approved by the USFDA in September 1998 as the first line treatment of HER2 overexpressing metastatic breast cancer. Later, it also received approval for the adjuvant treatment of HER2 overexpressing node-positive or node-negative breast cancer.

The field of breast tumor therapeutics is approaching yet another shift in paradigm - from treatment to prevention...

Until the 1970s, most of the efforts for confining solid tumor growth were focused on finding new ways to affect the proliferation and induce apoptosis within tumor cells. Although observations suggesting the importance of a supporting vasculature for tumor expansion were made as early as 1908 (46), the concept of preventing new blood vessel growth (angiogenesis) as an approach to contain tumor mass was not seriously considered until Judah Folkman proposed the theory (47) and began pursuing it experimentally. The pioneering studies in his laboratory not only provided the experimental framework for studying tumor angiogenesis but also helped in understanding the molecular mechanisms of action of several important pro- and anti-angiogenic molecules like vascular endothelial growth factor (VEGF). Despite the early clinical failure of the anti-angiogenic peptide endostatin, the anti-VEGF antibody bevacizumab (avastin) received approval by the USFDA in 2004 for the treatment of metastatic colon cancer and most forms of non-small cell lung cancer. Bevacizumab is a humanized monoclonal antibody that binds and inactivates the signaling molecule VEGF, preventing the formation of new blood vessels. In 2008, it also received accelerated approval from the USFDA against the recommendation of its own advisory committee, to be used in combination with paclitaxel for the treatment of HER2 negative breast cancer. Approval was based on the clinical demonstration of bevacizumab to reduce tumor volume and modestly increase progression-free survival despite its inability to significantly improve overall survival of the patients (48).

Because of the success of bevacizumab, several additional anti-vascular agents that act by specifically inhibiting VEGF function or by other means are currently being assessed at different stages of clinical trials (49). Success with even a few of them will increase the available treatment options and will ensure a more comprehensive clinical care for patients.

Prospects for the future

In the last 50 years, the trend in breast cancer drug-discovery has undergone a slow but steady shift from the development of cytotoxic agents to the design of targeted therapies based on increased understanding of the molecular and genetic components of tumor biology. The development of tamoxifen and other aromatase inhibitors marked the beginning of this trend, and the introduction of novel biologicals like trastuzumab, bevacizumab and other agents in the current clinical pipeline have advanced this trend into what might be termed a 'targeted therapy' revolution. Every new anticancer agent being developed by the pharmaceutical industry today is designed to target a tumor specifically, potentially reducing the toxicity for the patient. The transition from cytotoxic drugs to targeted therapies has certainly provided us with better drugs with fewer side effects. However, it has also presented us with new challenges. Most targeted therapies are effective only in a subset of patients. For example, trastuzumab is most effective against HER2 over-expressing tumors, and tamoxifen is most effective against tumors that express ERs. Therefore, molecular profiling and the identification of patients responsive to particular therapeutic regimes must become a central aim of cancer drug development in the coming decades (50). It has also become increasingly essential to effectively combat the problem of drug-resistance. Future clinical trials involving combinatorial use of targeted drugs and cytotoxic agents, together with intensive research to first discover and then suppress novel pathways involved in the development of drug resistance, will help us to partially overcome this problem.

The field of breast tumor therapeutics is approaching yet another shift in paradigm – from treatment to prevention – and the future seems even more promising in terms of cancer therapies. For instance, tamoxifen is leading the way in this shift, having recently been approved by the USFDA for reduction of breast cancer incidence in high-risk patients (29). Several recent clinical trials are now exploring the usefulness of various aromatase inhibitors as chemopreventive agents. The National Surgical Adjuvant Breast and Bowel Project (NSABP) will compare raloxifene with letrozole in their next clinical trial in postmenopausal women at high risk for breast cancer (51). The International Breast Cancer Intervention Group is currently comparing tamoxifen with anastrozole in a prevention study (52), and a three-arm prevention study organized by the National Cancer Institute of Canada (NCIC) will compare placebo versus exemestane versus exemestane and celecoxib (52) as preventative chemotherapies.

Whether or not we will be triumphant in the battle against cancer is a question that only time can answer. However, what is certain is the fact that our persistent efforts will allow us to extend the survival and improve the quality of life of cancer patients.

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