Biological drugs in breast cancer: increasing understanding for the pharmacist

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Keywords: biological drugs, breast cancer, novel therapeutic agents, trastuzumab, bevacizumab, lapatinib

Abstract
Cancer in South Africa is an emerging health problem, with breast cancer being a leading cancer in women. The medical treatment of breast cancer was solely reliant on cytotoxic chemotherapy for many years. A greater understanding of the underlying biology of breast cancer has resulted in the identification of a number of molecular targets and the development of novel therapeutic agents. Thus, treatment has evolved over the past decade into a more target-directed approach with the use of biological drugs. The three currently available biological drugs registered in South Africa for use in breast cancer include trastuzumab (Herceptin®), bevacizumab (Avastin®) and lapatinib (Tykerb®). This article briefly discusses their role in targeting breast cancer.

Introduction
Breast cancer is the most common cancer in women worldwide. Breast cancer was the second leading cancer following cervical cancer in South Africa. However, over the past three decades, it has emerged as the most common cancer in women.

Breast cancer is a disease in which malignant (cancerous) cells form in the tissue of the breast. It is considered to be a heterogeneous disease because it differs according to individual, age group and even the kinds of cells within the tumours itself.

There are several different types of breast cancer, depending on the part of the breast in which it develops. Breast cancer is often divided into non-invasive and invasive types. Non-invasive breast cancer is also known as cancer or carcinoma in situ. This cancer is found in the ducts of the breast and has not developed the ability to spread outside the breast. This form of cancer rarely shows as a lump in the breast and is usually found on a mammogram.

Invasive breast cancer has the ability to spread outside the breast.

It is possible for breast cancer to spread to other parts of the body, usually through the lymph nodes. If this happens, it is known as “metastatic” breast cancer.

The treatment of breast cancer involves the role of a multi-disciplinary team of specialists who take into consideration the stage of the cancer, among other variables, to determine the treatment strategy. The main treatment options for breast cancer include surgery, radiotherapy, chemotherapy, hormone therapy or biological therapy (targeted therapy).

Biological therapy can help to repair, stimulate or enhance the immune response since cancer may be the result of a malfunction of the immune system. Traditional cancer treatments, although effective, often have significant limitations. Biological drugs can target the cancer in a specific way and may work synergistically with chemotherapy to improve the outcome.

Biological drugs to target breast cancer
Although breast cancer is among the most chemosensitive of the solid tumours, important improvements in survival have been achieved over the past two decades with the introduction of newer agents. Increased knowledge of the genetic alterations, molecular subtypes and signalling pathways of breast cancer has facilitated the development of targeted therapies with the use of biological drugs.

Targeted therapy consists of targeting the malignant cell development pathway, including crucial processes involved in cell invasion, cell metastasis, cell cycle and tumour-related angiogenesis (the formation of new blood vessels). These targets have led to treatments that have demonstrated sophistication over conventional cytotoxic chemotherapy or hormone-based therapy.

Epidermal growth factor receptor (EGFR) and human epidermal growth factor receptor 2 (HER2) are frequently overexpressed in breast cancer and are associated with aggressive clinical behaviour and poor outcome. EGFR plays a major role in promoting breast cancer cell proliferation and malignant growth. HER2 is a member of the EGFR family and is overexpressed in approximately 15-25%
Angiogenesis, the process of new blood vessel formation, plays a central role in both local tumour growth and distant metastasis in breast cancer. Understanding these molecular processes has provided attractive targets for the following therapeutic interventions currently registered for use in South Africa:

- HER2-targeted therapy with trastuzumab
- Anti-angiogenic strategy with anti-vascular endothelial growth factor (VEGF) and bevacizumab
- Dual EGFR/HER2 inhibition with lapatinib.

These agents, in combination with chemotherapy, have proven to be a milestone in molecular targeted therapy for breast cancer.

**Trastuzumab**

Trastuzumab is a recombinant monoclonal antibody that binds to the HER2 receptor on the outside of the cell. This binding inhibits the proliferation in tumour cells that overexpress HER2. Trastuzumab (Herceptin®) is indicated for HER2-positive metastatic breast cancer as monotherapy for the treatment of patients who have received at least two chemotherapy regimens for their metastatic disease, in combination with paclitaxel or docetaxel for the treatment of patients who have not received chemotherapy for their metastatic disease and in combination with an aromatase inhibitor for the treatment of patients with hormone-receptor positive metastatic breast cancer.

Trastuzumab is also indicated for HER2-positive early breast cancer following surgery, chemotherapy [neoadjuvant (chemotherapy before surgery which is generally used to shrink a large tumour) or adjuvant (chemotherapy used after surgery to destroy any cancer cells that have not been removed)] and radiotherapy, if applicable.

**Efficacy**

Trastuzumab should only be used in patients whose tumours have HER2 overexpression, i.e. are HER2-positive. Clinical trial results have demonstrated that the use of trastuzumab improves median survival in such patients. Table I details the comparative survival results.

**Dose**

A loading dose of Herceptin® (4 mg/kg body weight) should be administered as a 90-minute intravenous infusion in metastatic breast cancer. The recommended weekly dose of Herceptin® is 2 mg/kg, beginning one week after the loading dose. Paclitaxel or docetaxel may be administered the day following the first dose of Herceptin®, or immediately after the subsequent doses of Herceptin®, if well tolerated.

An initial loading dose of Herceptin® (8 mg/kg body weight) should be administered in early breast cancer, followed by 6 mg/kg three weeks later, and then 6 mg/kg repeated at three-weekly intervals, administered as a 90-minute intravenous infusion. Patients with early breast cancer should be treated for one year or until disease recurrence.

**Safety**

Trastuzumab administration can result in the development of ventricular dysfunction and congestive heart failure. Left ventricular function should be evaluated in patients prior to and during treatment. The discontinuation of trastuzumab must be strongly considered in patients who develop a clinically significant decrease in left ventricular function.

Trastuzumab is contraindicated in patients with known hypersensitivity to trastuzumab or its excipients and severe dyspnoea at rest, owing to complications of advanced malignancy or the requirement for supplementary oxygen. Its safety has not been established in pregnancy and lactation.

A high risk of cardiotoxicity is associated with the use of trastuzumab, in combination with anthracycline antibiotics. Therefore, it should not be used concurrently, except in a well-controlled clinical trial setting with cardiac monitoring.

Approximately 50% of patients can be expected to experience adverse reactions when using trastuzumab for metastatic breast cancer. The most common adverse reactions are infusion-related symptoms, such as fever and chills, and usually occur after the first infusion of trastuzumab.

From the clinical trial data, the following adverse events were experienced at a higher incidence than others and were common to both treatment in metastatic breast cancer and early breast cancer:

- **General:** Headaches, asthenia, fever and chills
- **Gastrointestinal:** Diarrhoea, nausea and vomiting
- **Musculoskeletal:** Arthralgia and myalgia
- **Skin:** Rashes.

Herceptin® is available in a multi-dose vial containing 440 mg of trastuzumab which should be stored at 2-8°C. The reconstituted vial contains 21 mg/ml trastuzumab and is stable for 28 days when stored refrigerated at 2-8°C, but should not be frozen. The reconstituted vial contains a preservative and is therefore

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Monotherapy</th>
<th>Combination therapy</th>
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<tbody>
<tr>
<td>Trastuzumab</td>
<td>16.4</td>
<td>24.8</td>
</tr>
<tr>
<td>Trastuzumab plus paclitaxel</td>
<td>17.9</td>
<td>30.5</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>30.5</td>
<td>22.1</td>
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<tr>
<td>Docetaxel</td>
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suitable for multiple use. Solutions for infusion are stable in polyvinylchloride or polyethylene bags containing 0.9% sodium chloride at 2-8°C for 24 hours.12

**Bevacizumab**

Clinical evidence suggests that angiogenesis plays an essential role in breast cancer development, invasion and metastasis by increasing the vasculature (number of blood vessels) of a tumour. VEGF is essential for the development of new blood vessels at very early stages of the development of a tumour. Therefore, it has been suggested that it plays a major role in the formation of tumour metastasis.7

Bevacizumab is a recombinant monoclonal antibody that selectively binds to and neutralises the biological activity of VEGF. Neutralising the biological activity of VEGF reduces the vascularisation of tumours, thereby inhibiting tumour growth.13

Bevacizumab (Avastin®) is indicated in combination with paclitaxel as first-line treatment in patients with locally recurrent or metastatic breast cancer.13

**Efficacy**

Bevacizumab was registered in combination with paclitaxel as the first-line treatment option for locally recurrent or metastatic breast cancer. It has demonstrated improved progression-free survival and overall response rates compared with monotherapy8 (Table II).

<p>| Table II: Progression-free survival and overall response rates of bevacizumab in breast cancer |</p>
<table>
<thead>
<tr>
<th>Results</th>
<th>Bevacizumab plus paclitaxel</th>
<th>Paclitaxel monotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progression-free survival (months)</td>
<td>11.8</td>
<td>5.9</td>
</tr>
<tr>
<td>Overall response rate</td>
<td>36.9%</td>
<td>21.2%</td>
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</table>

**Dose**

The recommended dose of bevacizumab is 10 mg/kg of body weight given once every two weeks or 15 mg/kg of body weight given once every three weeks as an intravenous infusion.13

**Safety**

Bevacizumab is contraindicated in patients with known hypersensitivity to any components of the product and those with untreated central nervous system metastases.13 It must not be used during pregnancy. Women must not breastfeed during bevacizumab treatment and for at least six months after the last dose.

The overall safety profile of bevacizumab is based on data from clinical trials. The most serious side-effects are:

- Gastrointestinal perforations
- Haemorrhage, including pulmonary haemorrhage and haemoptysis
- Arterial thromboembolism.

Bevacizumab is available in vials containing 25 mg/ml of active ingredient. Avastin® 100 contains 100 mg bevacizumab per 4 ml and Avastin® 400 contains 400 mg bevacizumab per 16 ml.

Avastin® does not contain any antimicrobial preservative. Therefore, care must be taken to ensure the sterility of the prepared solution. Chemical and physical in-use stability has been demonstrated for 48 hours at 2-30°C in a 0.9% sodium chloride solution. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user (normally not for longer than 24 hours at 2-8°C), unless dilution has taken place in controlled and validated aseptic conditions.13

**Lapatinib**

Lapatinib is a potent, reversible and selective inhibitor of both EGFR and HER2 receptors.14 It is currently the most advanced agent because of its dual receptor action. The rationale behind the dual EGFR/HER2 action is to sustain the synergistic inhibition of the cancer cells. Lapatinib (Tykerb®) exhibits a slow dissociation rate from EGFR, resulting in a prolonged effect.8

Laptinib is indicated in combination with capecitabine for the treatment of patients with metastatic breast cancer whose tumours overexpress HER2 and who have received prior therapy, including trastuzumab.14

**Efficacy**

Laptinib was registered in combination with capecitabine for the treatment of patients with HER2-positive metastatic breast cancer. Results from clinical trials showed a 51% risk reduction of disease progression compared to monotherapy with capecitabine8 (Table III).

<p>| Table III: Efficacy results of lapatinib in breast cancer |</p>
<table>
<thead>
<tr>
<th>Results</th>
<th>Lapatinib plus capecitabine</th>
<th>Lapatinib</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median time to tumour progression (months)</td>
<td>8.4</td>
<td>4.4</td>
</tr>
<tr>
<td>Overall response rate</td>
<td>22.5%</td>
<td>14.3%</td>
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</table>

**Dose**

The recommended dose of lapatinib is 1 250 mg (i.e. five tablets) once daily continuously. Tykerb® should be taken at least one hour before or at least one hour after food.14

**Safety**

Diarrhoea, including severe diarrhoea, has been reported with lapatinib treatment. The proactive management of diarrhoea with anti diarrhoeal agents is important. Severe cases of diarrhoea may require the administration of oral or intravenous electrolytes and fluids, and interruption or discontinuation of therapy with lapatinib.14
Lapatinib has been associated with reports of decreases in left ventricular ejection fraction, interstitial lung disease and pneumonitis, and hepatotoxicity.\textsuperscript{14}

Lapatinib is predominantly metabolised by cytochrome enzymes. Therefore, inhibitors or inducers of these enzymes may alter the pharmacokinetics of lapatinib. Concomitant administration with such agents should proceed with caution and the clinical response and any adverse events carefully monitored.\textsuperscript{14}

Very common adverse events include fatigue, anorexia, diarrhoea, rashes, dry skin, dyspepsia and insomnia.\textsuperscript{14}

Tykerb® is available as a film-coated tablet containing 250 mg lapatinib ditosylate monohydrate.\textsuperscript{14}

Internationally, there are even more biological treatment options for breast cancer. As data become mature, more biological agents may become available in South Africa. Although most pharmacists are not routinely consulted on oncology drugs, it is important to understand the innovation and development behind the evolution of treatment for breast cancer.

**Conclusion**

The most recent major contribution to the treatment of breast cancer has not been a technological or pharmacological revolution, but a transformation in the way in which the disease and treatment are viewed. Three biological drugs are registered for use in breast cancer in South Africa. Clinical trials are constantly being conducted whereby other molecules are being identified and which demonstrate an improvement in survival rates and disease progression. An increasing number of biological agents are being registered internationally. This disease area is constantly being investigated in the hope of discovering newer target sites for drug development through an understanding of breast cancer at molecular and genetic level. Although breast cancer remains an incurable disease, promising strides are being made, through the ongoing development of biological targeted therapies, in reducing mortality rates and improving survival rates in patients with breast cancer.

**References**