**Case presentation**

A 45-year old woman was diagnosed in October 2005 with stage IIB right breast cancer (BC). She underwent a right radical mastectomy with axillary lymph nodes dissection. Pathology revealed an infiltrative ductal carcinoma • Scarff and Bloom Grade II • Tumor size of 3 cm • 1 out of 13 lymph nodes was positive for metastasis • Estrogen and progesterone receptors were negative. Her2 level was over-expressed with 3+ on immunohistochemical staining and re-confirmed positive on FISH.

The patient received adjuvant chemotherapy with 6 cycles of FEC 100 regimen followed by adjuvant breast radiation and then Trastuzumab 6 mg/kg every 21 days for 1 year which ended in December 2007.

In September 2008, the patient had a disease relapse with multiple lungs, liver and bone metastases. She received first line treatment with Trastuzumab/Docetaxel/Vinorelbine/Zoledronic acid for 10 months. She developed a partial response with a time to progression of 11 months.

In August 2009, she developed a progressive disease with brain metastases treated with whole brain radiation (30 Gy in 15 fractions) followed by 3 cycles of Trastuzumab/Capecitabine/Zoledronic acid.

In January 2010, restaging scans showed progressive disease and she started another salvage chemotherapy regimen with Lapatinib/Gemcitabine/Carboplatine/Zoledronic acid. Her last evaluation was performed in September 2010 showing a partial response, her Performance Status is 0 and no grade 3-4 toxicities.

**Discussion**

BC is the most common female cancer and the second most common cause of cancer death in women [1]. In Lebanon, BC is also the most common cancer in women representing about 38% of all female cancer cases [2]. Approximately 18 to 20 percent of BC overexpress HER2, a transmembrane glycoprotein receptor with tyrosine kinase (TK) activity. The expected 5-year survival rate of stage IIB BC patients such as our patient is 74% [3].

Different treatment modalities and multiple drug options are available for metastatic breast cancer (MBC) patients. The selection of therapeutic strategy depends upon tumor biology, clinical factors, patient and physician preferences as well as socioeconomic factors.

Response to endocrine therapy is infrequent for patients with ER-/PR-tumors (less than 10%) [4]. However, a response to endocrine therapy does occur, possibly as a result of false negative ER analysis [5].

High levels of HER2 overexpression identify patients who might benefit from drugs that target HER2, such as trastuzumab and lapatinib.

There is no “one size fits all” approach to selecting optimal chemotherapy treatment for women with ER-/PR-MBC. The choice of chemotherapeutic agents and single agent use v/s combination depend on multiple factors including the specific side effects of the drugs, the site of metastases, the pace of disease progression as well as physician and patient preferences. Some patients are willing to accept a high burden of toxicity for small survival benefits, while others may only wish to be treated if toxicity is minimal and the likelihood of symptom control is high [6].

The socio-economic status of our patient and the availability of chemotherapy...
and targeted therapy at the ministry of Public Health of Lebanon dictated part of the choices and the timing of the use of this sequential combination protocols.

Standard first line treatment of MBC with ER/PR-; Her2+ is a combination of trastuzumab with chemotherapy.

The benefit of first-line trastuzumab monotherapy was studied in 114 women with newly diagnosed MBC who were randomly assigned to one of two dose levels of trastuzumab (4 mg/kg initially followed by 2 mg/kg weekly or 8 mg/kg to start followed by 4 mg/kg weekly) [7]. The overall response rate was 35% for women with 3+ IHC. There was no clear dose-response relationship for objective response rate, survival, or adverse events.

An every three-week administration schedule with 8 mg/kg loading dose followed by 6 mg/kg every 21 days was also studied in a large phase II trial and showed to be active, well tolerated, and increases patient convenience [8]. Based on these data, an every 3 weeks trastuzumab regimen was considered as the cornerstone treatment of Her2+MBC.

Preclinical studies suggest additive and synergistic interactions between trastuzumab and multiple cytotoxic agents including anthracyclines, taxanes, platinum analogs, vinorelbine, capecitabine and cyclophosphamide [9]. The addition of chemotherapy to trastuzumab results in a significant increase in response rate 50% v/s 32% (p < 0.001), time to progression 7.4 v/s 4.6 months (p < 0.001); HR = 0.51 CI [0.41- 0.63] and median survival 25.1 v/s 20.3 months p = 0.046; HR = 0.8 [0.64- 1.00] [10].

In a phase III trial, 107 patients were randomly assigned to trastuzumab plus docetaxel or trastuzumab alone. The addition of docetaxel to trastuzumab resulted in significantly superior progression-free survival and overall survival (HR 2.72) [11]. Adding another chemotherapeutic agent does not seem to be of more benefit. In the BCIRG 007 trial [12], 233 Her 2 positive MBC patients were randomly assigned to Trastuzumab/Docetaxel v/s Trastuzumab/Docetaxel/Carboplatin Objective response rate was similar in both arms (72%). There were no significant difference in both TTP (11.1 v/s 10.3 months) and overall survival.

Nevertheless, one interesting SWOG study showed an impressive survival with the combination of Trastuzumab/Docetaxel/Vinorelbine with a RR of 71%, a PFS of 19 months and an OS of 39 months [13].

For patients with BC and bone metastases, bisphosphonate therapy can prevent and/or delay skeletal complications, prevent chemotherapy-related bone loss and palliate bone pain. A survival benefit has not however been shown [14].

A meta-analysis of nine trials, which included 2189 women with MBC and bone metastases, showed that intravenous bisphosphonates reduced the risk of developing a skeletal event by 17% (HR 0.83; 95% CI [0.78-0.89]) [14]. The duration of benefit for monthly bisphosphonates in women with osteolytic bone metastases is unknown. Drug administration for at least six months is typically necessary before an effect is seen on skeletal morbidity outcomes [15].

Taking all these data in consideration as well as our patient young age and preferences, we decided to start first line treatment with Trastuzumab/Docetaxel/ Vinorelbine/Zoledronic acid and G-CSF support.

Approximately one-third of women receiving trastuzumab for Her2 positive
MBC will develop brain metastases [16]. One explanation of this high incidence of brain metastases in this category of patients would be the lack of trastuzumab penetration into the CNS, coupled with prolonged control of what was previously rapidly lethal systemic disease. This might lead to reveal brain metastases that would otherwise have remained clinically silent [17].

Treatment options for brain metastases include surgical resection, stereotactic radiosurgery, whole brain radiation (WBRT) or combination of modalities. The choice of modality depends on the patient performance status, systemic disease control, number of brain lesions and potential resectability. Randomized clinical trials have generally demonstrated that WBRT in addition to either surgery or SRS improved local control but has no impact on overall survival [18]. Since the patient had multiple disseminated brain metastases, we opted for WBRT as a sole option of controlling her brain disease.

Continuation of trastuzumab after progression on first line treatment with trastuzumab-containing regimen is safe and effective. The benefit was suggested by a retrospective study [19] and confirmed by a German trial which randomized 156 women with MBC patients who progressed during treatment to capecitabine alone or in combination with trastuzumab. Continuation of trastuzumab was associated with a significantly longer median time to progression and an improvement in overall survival [20].

Lapatinib is an orally active dual EGFR and Erb2 inhibitor with limited serious toxicities.

The benefit of lapatinib in heavily treated patients was shown in a phase III trial of 324 women with progressive, HER2-overexpressing MBC who were previously treated with an anthracycline, taxane and trastuzumab [21]. This trial randomized patients to capecitabine or capecitabine and lapatinib. There was a significant benefit in TTP 6.2 v/s 4.3 months ($p < 0.001$) HR = 0.57 [0.43-0.77]. Fewer patients in the lapatinib group developed brain metastases as the first site of progression 13 versus 4% ($p = 0.045$). There was however no significant benefit on survival 15.6 v/s 15.3 months ($p = 0.177$) HR = 0.78 [0.55-1.12]. The combination was also safe. Diarrhea and rash occurred more frequently in the combination group with the difference due to an increase in grade 1 events. The treatment was discontinued for adverse events in 14% of patients in each treatment group. There were no differences in mean LVEF values between the two groups at scheduled assessments.

Another interesting strategy of the use of lapatinib is a dual inhibition of Her2 receptor by combining it with trastuzumab. A phase III trial of 296 women with MBC progressing on prior trastuzumab-containing regimens randomized patients to lapatinib or lapatinib and trastuzumab [22]. The combination resulted in a significant improvement in clinical benefit rate 24.7% v/s 12.4% ($p = 0.01$) and progression-free survival (HR = 0.73 [0.57-0.93] ($p = 0.008$).

Lapatinib is also an attractive option for our patient when compared to trastuzumab since it can cross the blood brain barrier. CNS response rate can be up to 20% [23]. Patients receiving lapatinib have also a significant fewer CNS events [21].

One possible future promising drug that can be used eventually later on at disease progression is T-DM1. T-DM1 is an antibody-drug conjugate designed to combine the biological activity of trastuzumab with the targeted delivery of a high-
ly potent anti-microtubule agent (DM1) to HER2-expressing cells.

In a Phase II study, 110 women with HER2-positive advanced breast cancer whose disease had worsened after receiving at least two prior HER2-targeted treatments (Trastuzumab and lapatinib) in the metastatic setting, as well as an anthracycline, a taxane and capecitabine received T-DM1 drug. Response rate was 33%. Severe toxicities were limited to thrombocytopenia (7%) [24-25]. FDA submission of this drug was based upon this amazing data.

Conclusion

In summary, metastatic Her-2/neu breast cancer patients have seen their prognosis and therapeutic options substantially improving in the last decade.

The incorporation of trastuzumab and lapatinib in the treatment protocols has led to the emergency of multiple algorithms treatments. Their use in combination and the recent introduction of antibody-drug conjugates seem to be promising.

References

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