ABSTRACT

Background: Her-2/neu positive breast cancer is an aggressive disease with a higher potential of invasion and metastasis. It constitutes around 20% of all breast cancer cases and even a higher incidence has been reported in Egypt. Agents targeting Her-2 have been shown to be associated with improvement in response rate, disease free and overall survival.

Diagnosis: Different biomarkers have recently emerged to predict the benefit of trastuzumab and/or lapatinib. Phosphatase and tensin homolog (PTEN), topoisomerase 2 alpha (TOPO2A) and p95HER2 have been associated with appealing results in selecting patients who may or may not respond to these agents.

Results and Conclusion: Despite the impressive results of Her-2/neu targeting agents in both the adjuvant and metastatic phases, still a significant fraction of patients are not offered these agents particularly those in countries with limited resources due to their high cost. In this review, we will discuss how we can optimally use these agents from a developing nation perspective. We will elaborate on different schedules available and will highlight the importance of incorporating different biomarkers to assist in proper selection of patients who can optimally benefit these agents.

Key Words: Trastuzumab – Lapatinib – Her-2/neu – Predictive factors – Developing nations – PTEN.

INTRODUCTION

Breast cancer is the most common malignant tumor diagnosed in women all over the world; yet its incidence differs from one region to another. In the Arab countries including Egypt, breast cancer constitutes around 13-35% of all female cancers [1]. The median age tend to be younger than that of the western countries with almost half of the patients diagnosed below the age of 50.

Her-2/neu-positive tumors account for approximately 20% of all breast cancers and these tumors carry poor prognosis [2]. This incidence is even higher in Egypt in which the incidence reaches as high as 40% in some studies [3]. In Her-2/neu positive breast cancer, Her-2 receptor is believed to be the main driving force responsible for tumor cell proliferation, metastatic potential and poor survival [2]. Accordingly, therapeutic targeting of Her-2/neu has the potential benefit to offset the signaling process initiated by the Her-2 over-expression, thus reversing the malignant features of these tumors.

Currently, two drugs are approved to target the Her-2/neu gene in breast cancer; trastuzumab and lapatinib. Despite their significant activity in this setting, it has been shown that a significant proportion of patients do not derive any benefit from either agents or even both in spite of having a Her-2/neu positive tumor. Moreover, it is still unclear how to optimally use these drugs. These issues are of major importance particularly for countries with limited resources. Here, we will discuss the different schedules reported and possible mechanisms of resistance in addition to potential biomarkers that could predict response to these agents in an attempt to guide oncologists; particularly those in developing nations on how to optimize their use in breast cancer.
TRASTUZUMAB

Trastuzumab is the first agent developed to target the Her-2/neu pathway. It is a humanized monoclonal antibody that recognizes a certain epitope along the extracellular domain (ECD) of Her-2. It inhibits tumor cell growth in vitro and in vivo via 2 mechanisms. The first is downregulation of Her-2-induced nuclear signaling through inhibition of the PI3K/Akt pathway. In this aspect, trastuzumab stabilizes and activates PTEN [4], a natural inhibitor of the PI3K/Akt pathway [5], leading to accumulation of p27kip1, which induces cell cycle arrest at the G1 phase and enhances apoptosis of tumor cells. A second mechanism is through an antibody-dependent cell-mediated cytotoxicity. In this aspect preclinical studies have shown that trastuzumab efficacy could be related to the induction of immune response against Her-2 protein [6].

Trastuzumab is used in the management of adjuvant as well as metastatic breast cancer over-expressing Her-2. In the metastatic setting, the addition of trastuzumab to chemotherapy has shown to improve all treatment endpoints [7]. In the adjuvant setting, several studies were conducted to test the role of trastuzumab in the adjuvant setting [8-11]. The results showed that the addition of trastuzumab to adjuvant chemotherapy reduces the risk of relapse by around 50% with a one third reduction in mortality; a magnitude of benefit not previously encountered by any drug in breast cancer treatment. Nevertheless, several points remain to be determined including the duration of trastuzumab in the adjuvant phase as well as its scheduling in relation to chemotherapy.

The optimal duration of trastuzumab in the adjuvant setting is still unclear. Four large studies administered the drug for one year [8-10]. While this approach proved to be very effective as mentioned, still the long duration of administration is of concern given the very high cost of the drug and its potential cardiac toxicity. Trastuzumab costs around 70,000 $ for a one-year course [12], which represents a real burden on health care systems. It also poses a significant risk of cardiac toxicity. In the Breast Cancer International Research group (BCIRG) 006 [9] and the Intergroup [10] adjuvant studies, the addition of one year of trastuzumab increased the risk of grade III and IV cardiac toxicity by 3 to 4 times compared to placebo. The FinHer study argued against the need for prolonged treatment with trastuzumab [11]. They demonstrated that adding nine weeks of this drug to chemotherapy was significantly superior to chemotherapy alone. The magnitude of benefit appeared similar to that of the one-year schedule; despite that the patients’ characteristics’ were similar. Furthermore, there was no grade III or IV cardiac toxicity encountered at all, which was reasoned by the short treatment period as well as administration of trastuzumab before anthracyclines. Thus it could be hypothesized that a short course of trastuzumab (9 weeks) could be enough to achieve the maximum benefit of the drug and thus avoiding unnecessary life threatening cardiac toxicity and inconveniently long treatment periods, which leads to significantly more added expenses. Only one study (E2198) has directly compared the 9-weeks of adjuvant trastuzumab to the one-year schedule [13]. In this study, Sledge and colleagues randomized 234 patients between the two arms. At a median follow-up period of 64 months, the five-year disease free and overall survival was equivalent in both arms. Despite that the trial was not powered to detect a difference in survival, the results remain impressive. Several clinical trials are currently ongoing by the Hellenic Oncology Research group (NCT00615602), NCI Paris (NCT00381901) and an Italian group (NCT00629278) to directly compare 6 versus 12 months of trastuzumab in the adjuvant setting.

The timing of trastuzumab in relation to adjuvant chemotherapy remains arguable as well. Trastuzumab was given either concomitantly or sequentially after chemotherapy. In two trials [9,11], trastuzumab was given in combination with chemotherapy while in the HERA trial the drug was given sequentially following chemotherapy [8]. The Intergroup study was the only one to directly compare both approaches with clear superiority of the concomitant arm [10]. Actually in this particular study, compared to "no trastuzumab" arm, there was no significant benefit of trastuzumab when given following the end of chemotherapy. This was further demonstrated in the PACS-04 study [14] where patients randomised to the sequential trastuzumab arm did exactly the same like those who did not receive trastuzumab at all. This fact emphasizes the importance of the synergistic role of trastuzumab when added to chemotherapy as
previously shown in pre-clinical models in order to enhance chemotherapy induced apoptosis. Thus, available evidence appears in favour of the concomitant application of trastuzumab with chemotherapy.

The optimal chemotherapeutic regimen used in combination with trastuzumab in terms of efficacy is another issue that deserves emphasis. The BCIRG 006 study gave some important answers in this concern [9]. In this study, the addition of trastuzumab to either docetaxel/carboplatin (TCH) or AC/docetaxel (AC→TH) produced significant reduction in breast cancer relapse and mortality compared to chemotherapy alone. However subgroup analysis according to TOP2A co-amplification (30% of the whole group) has shown that the magnitude of benefit of trastuzumab in AC→TH arm was similar to TCH arm when TOP2A gene was not co-amplified. But, in TOP2A positive cases, the disease free survival of all the 3 groups was exactly the same (i.e. the addition of trastuzumab didn’t improve DFS in this subgroup). A systematic review of all the adjuvant studies was conducted by Slamon and colleagues [15], which further confirmed that in TOPO2A co-amplified tumors, anthracyclines alone (i.e. without trastuzumab) would probably be enough.

Her-2/neu positive breast cancer has a ten times higher incidence of brain metastases compared to Her-2/neu negative tumors [16]. It has been postulated that an interaction between chemokine receptor (CXCR4) and its ligand stromal cell derived factor 1 alpha allows breast cancer cell migration through human brain microvascular endothelial cells. This interaction has been shown to be essential for development of brain metastasis [17]. As trastuzumab is a large molecule that can not cross the blood brain barrier, brain metastasis has been a devastating sanctuary site for these patients. In a previous study conducted by our group [18], 32% of patients treated with trastuzumab in the metastatic setting developed brain metastases at a median time of 14 months. This group had a median survival of 26 months which was significantly inferior to those who did not develop brain metastasis. Thus the lack of activity of trastuzumab in this setting represents a real drawback.

Several biomarkers have emerged as potentially useful in predicting the response to trastuzumab. Patients who have PTEN positive tumors have been shown to derive the maximum benefit of trastuzumab compared to those with PTEN negative tumors. In a small clinical trial conducted by Nagata and colleagues, 47 patients with Her-2/neu positive breast cancer were treated with trastuzumab and paclitaxel. Those who had a high expression of PTEN had a response rate (PR and CR) around 70% compared with less than 20% for those with negative PTEN expression [19]. These results were further demonstrated by Fujita and colleagues who reported a response rate of 89% for PTEN positive tumors versus 12.5% for PTEN negative tumors (p=0.00337) [4]. The presence of truncated receptors (p95HER2) have been lately been quoted as a potential predictor marker for trastuzumab resistance. In a recently reported retrospective analysis, patients with truncated Her-2/neu had an 11% very response rate to trastuzumab-based therapy compared to 51.4% to those with tumors expressing full-length Her-2 (p=.029) [20].

**LAPATINIB**

Lapatinib is an oral small molecule dual inhibitor of the Her-1 and Her-2 tyrosine kinase (TK), which directly inhibits kinase activity of both receptors. Although, it blocks Her-1 and Her-2 TK with the same potency, its therapeutic benefit is only seen in breast cancer over-expressing Her-2/neu rather than Her-1 [21,22].

Lapatinib received the FDA approval in March 2007 after the impressive results shown by Geyer and colleagues in heavily pretreated Her-2/neu positive breast cancer patients [23]. In the EGF100151 phase III trial, 321 patients with Her-2/neu positive tumors who have previously failed trastuzumab therapy were randomized to single agent capecitabine or in combination with lapatinib. In the combination arm, time to progression was almost doubled compared to capecitabine alone (p-value: 0<0.001). This was achieved without any significant increase in serious adverse events. Moreover, a recently reported trial demonstrated that patient who failed trastuzumab can achieve a considerable benefit of single agent lapatinib with a clinical benefit in the range of 25% [24]. Thus, both studies clearly confirm the absence of cross resistance between both agents.
The dosing of lapatinib has recently been an area of debate. In the previously mentioned studies, lapatinib was administrated at a dose of 1500mg/day. However, a recent study has clearly shown that a similar magnitude of benefit could be achieved with a lower dose of 1,000mg/d [25]. The adoption of the lower dose would save around 1000 $ per month which would probably result in a larger number of patients, who can receive the drug particularly in countries with limited resources.

Unlike trastuzumab, lapatinib is a small molecule that can cross the blood brain barrier. In the EGF100151 pivotal study [23], patients who received lapatinib had significantly lower incidence of brain metastasis compared to those who received capecitabine alone. Moreover, in a phase II study involving patients with progressive brain metastasis following brain irradiation, lapatinib demonstrated a considerable activity with a median time to progression around 3 months [24]. Palmieri and colleagues went on to propose that lapatinib could even prevent the evolution of brain metastasis [25]. They hypothesized that lapatinib inhibits brain colonization of dual Her-1/Her-2 over-expressing breast cancer cells. Currently two large studies (ALT-TO and TEACH) are investigating the role of lapatinib in the adjuvant phase and its effect on reducing the incidence of brain metastasis.

Another unique difference between lapatinib and trastuzumab is their effect on the heart. Trastuzumab have been shown to be associated with considerable cardiotoxicity particularly in the presence of doxorubicin [7]. This is obviously not the case with lapatinib. In a unique work by Perez and colleagues, they analyzed the cardiac safety of lapatinib in more than 3500 patients enrolled in clinical trials [26]. In this large analysis, only 1.6% of cases developed a cardiac adverse event; which were mostly asymptomatic, with reversible decrease in left ventricular ejection fraction occurring at similar rates in patients who were and were not pre-treated with anthracyclines or trastuzumab.

Little is known regarding how to predict response to lapatinib. Patients with truncated Her-2/neu (i.e. no ECD) are likely to benefit lapatinib rather than trastuzumab. Preclinical models have shown that tumors expressing p95HER2 are resistant to trastuzumab but not lapatinib [20]. Recently, Cameron and colleagues have shown that resistance to lapatinib is not related to expression of p95HER2 [29]. Moreover, the antitumor effects of lapatinib on Her-2/neu-overexpressing breast cancer cells appear to be closely linked to the down-regulation of survivin [30]. Although inhibition of Her-2 autophosphorylation and signaling via MAPK and PI3K/Akt pathways may be necessary for clinical response to lapatinib, yet, it is not sufficient [21]. In this context, Gomez and colleagues have recently failed to demonstrate any correlation between response to single agent lapatinib and PTEN expression [25].

**CONCLUSIONS**

Trastuzumab and lapatinib, while their discovery represents a milestone in treating Her-2/neu positive breast cancer, it is obvious that still a significant proportion of patients will not derive any benefit despite over-expressing Her-2. Moreover, the lack of cross resistance could hypothesize that certain patients will derive a benefit from one drug rather than the other.

In nations with limited economy like Egypt, offering adjuvant trastuzumab remains a challenge, yet the FinHer model could serve as a more feasible approach. It is still unknown whether longer duration of trastuzumab is really needed pending the results of the 2-year trastuzumab in the HERA study. If the results turned out to be negative, we believe that there will be more interest in exploring shorter schedules of adjuvant trastuzumab. The direct comparison in the E2198 study is reassuring acknowledging the limited sample size of the study.

Based on the data that have been discussed, patients with co-amplification of TOPO2A, expression of p95HER2, or negative PTEN seems to derive less benefit of trastuzumab and identifying these patients seems essential especially when resources are scarce. In cases of brain metastasis, lapatinib could serve as a better alternative. Offering lapatinib in a dose of 1,000mg/d seems more rationale given the absence of strong evidence to favor the higher dose.

In the era of targeted agents, better understanding of the molecular biology of different tumors could indeed guide oncologists on how to select the patients who would likely to benefit these effective; yet very expensive medications.
A problem remains in the absence of a standardized method for assessing biomarkers and in our opinion, this is desperately required. We are in urgent need for incorporating these different biomarkers in large scale studies to validate their predictive value on prospective basis.

REFERENCES


lapatinib for HER2-overexpressing advanced or metastatic breast cancer that progressed on first- or second-line trastuzumab-containing regimens. Ann Oncol. 2009, E-pub ahead of print.


