The Breast 22 (2013) 1009–1018

Contents lists available at ScienceDirect

The Breast

journal homepage: www.elsevier.com/brst

Review

Biological therapies in breast cancer: Common toxicities and management strategies

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ARTICLE INFO

Article history:
Received 21 May 2013
Received in revised form
14 September 2013
Accepted 21 September 2013

Keywords:
Breast cancer
Adverse events
Trastuzumab
Pertuzumab
Lapatinib
Bevacizumab
Trastuzumab-emtansine
Everolimus

ABSTRACT

In recent years, a number of new molecules – commonly known as biological therapies – have been approved or are in late stages of regulatory evaluation for the treatment of advanced breast cancer. These innovative compounds have improved treatment efficacy and have probably contributed to the increase in survival length observed in some breast cancer subtypes. However, these agents are not deprived of toxicity, which can impair quality of life and may occasionally be life-threatening. In this article, we reviewed the most common toxicities associated with these drugs and provided a number of practical recommendations on their optimal clinical management.

Introduction

Currently, six drugs entitled targeted or 'biological' agents are approved for clinical use in distinct disease scenarios in breast cancer (BC) management. The medications include trastuzumab, pertuzumab, lapatinib, trastuzumab-emtansine, bevacizumab and everolimus. These drugs are changing survival outcomes in metastatic BC patients and are largely used in clinical practice.

However, treating patients for longer periods with potentially toxic agents raises new challenges, such as managing their potential adverse events (AEs). Clinicians must be aware that gains in disease control and/or survival must be weighed against potential detrimental effects in quality of life (QoL). Some of these molecules can cause unusual AEs even for an experienced oncologist. Also, potentially life-threatening AEs can also occur. A recent meta-analysis showed that new anticancer agents approved since 2000 increased morbidity and treatment-related mortality [1]. Therefore, community oncologists must become fully familiar with the potential toxicity associated with these agents and must have the expertise for their appropriate management.

The objectives of this review are to provide 1) an updated description of the safety profile of novel targeted agents used in the management of breast cancer; 2) practical recommendations on the management of these AEs and patient monitoring.

Search criteria

We conducted an English-language MEDLINE (last 10 years) and proceedings of ASCO Annual Meetings and San Antonio Annual Meeting (last 5 years). We gave priority to phase III studies when those were available, but also included Phase II trials, when Phase III were not available. The search terms included six agents now approved or under evaluation from regulatory authorities. The last search was updated on 03 March 2013.

Abbreviations: ABC, advanced breast cancer; QoL, quality of life; AE, adverse event; HER2, human epidermal growth factor receptor type 2; LVEF, left ventricular ejection fraction; EGFR, epidermal growth factor receptor; T-DM1, Trastuzumab emtansine; FDA, Food and Drug Administration; VEGF, vascular endothelial growth factor; mTOR, the mammalian target of rapamycin; CT, computed tomography; RCC, renal cell cancer.

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http://dx.doi.org/10.1016/j.breast.2013.09.009

Trastuzumab

Risk of cardiac dysfunction

Approximately 15–20% of breast cancers have amplification or overexpression of the human epidermal growth factor receptor type 2 (HER2) and are characterized by an aggressive clinical behavior and a worse prognosis [2]. Trastuzumab, a humanized monoclonal antibody against HER2 was proven to be effective in several clinical trials in the neoadjuvant, adjuvant and metastatic setting [3]. However, in the Pivotal Trial that evaluated this drug, Trastuzumab use was associated with cardiac dysfunction, especially in the cohort of patients that were treated concurrently with anthracyclines [3]. Of note, cardiac monitoring was not mandatory in this trial and the actual risk of trastuzumab-related cardiac dysfunction remained unclear.

Subsequent studies demonstrated symptomatic heart failure (HF) in approximately 4% of patients [4–6]. An important adjuvant trial evaluated trastuzumab given sequentially to anthracyclines (4 cycles of Doxorubicin plus Cyclophosphamide followed by Docetaxel and Trastuzumab: AC-TH). This study included an arm of patients treated with Docetaxel plus Carboplatin plus Trastuzumab (TCH) and a third one with AC-T. The actual risk of symptomatic congestive heart failure was 2% for the AC-TH group and 0.7% for the TCH group of patients ($p < 0.001$). A subclinical asymptomatic loss of mean LVEF (defined as >10% relative loss) was found in 18.6% and 9.4% for the group that received AC-TH and TCH, respectively. This is showed in Table 1 [7].

Of note, Quality of Life data was collected in a portion of the patients from BCIRG006. Patients answered The European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire C30 and BR-23 at baseline, in cycle 4 and in the end of chemotherapy. The questionnaire was also answered at month 6, 12, and 24 after chemotherapy. Systemic side effect change scores were significantly improved for the group treated with TCH, compared with AC-TH and AC-T. All patients recovered from deterioration of systemic side effects by one year. This analysis suggests TCH as a more tolerable treatment [8]. Although TCH was associated with few cardiac events and better quality of life, one cannot conclude that this is a preferable regimen over AC-TH, as the trial was not designed to demonstrate it.

Asymptomatic impairment of left ventricular ejection fraction (LVEF) of 10–15% or more was seen in up 18% of patients as summarized in Table 1 [7,9–11]. The clinical significance of this finding remains unknown. Whether or not the cardiac toxicity rates can be generalized to the real world is still a matter of debate, since women included in these clinical trials were usually highly selected, with limited comorbidities. In addition, many studies simply excluded patients with suboptimal cardiac function. For instance, two recent retrospective studies performed in patients treated in the community setting suggested that risk of trastuzumab-associated cardiac dysfunction could be slightly higher than reported in the adjuvant trials [12,13]. It is also important to point out that LVEF decrease criteria can vary and the methods currently used to evaluate LVEF are quite heterogeneous among the clinical trials, As a consequence Trastuzumab Cardiac Toxicity can be over or underestimated depending on the criteria adopted.

Table 1
Reported asymptomatic LVEF and CHF in pivotal trastuzumab-based adjuvant trials in breast cancer.

Trial	Number of patients	LVEF decreasing	CHF
NSABP-31 [11,16]	1736	14.0%	4.1%
NCCTG 9831 [11]	1633	NR	2.9%
HERA [10]	3387	7.1%	1.7%
BCIRG 006[a] [7]	3222	18.6% × 9.4%	2.0% × 0.4%
FinHer [9]	332	3.5%	0.0%

Abbreviations: LVEF, left ventricular ejection fraction (defined as a drop in Left Ventricular Ejection Fraction of more than 10 units percent or a drop below 50%); CHF, congestive heart failure.
[a] Trastuzumab-based chemotherapy including or not anthracyclines.

Trastuzumab-related cardiotoxicity, differently from anthracycline-related, commonly presents as asymptomatic impairment of LVEF, does not appear to be related to cumulative dose and is often partially reversible with treatment interruption. Resuming treatment with trastuzumab after cardiac function recovery is often feasible. However it can also be associated with relapse of LVEF decrease [14]. To date, other anti-HER2 targeted agents have not been associated with significant cardiotoxicity.

Recommendations for the management of trastuzumab-related cardiotoxicity

The most important risk factors for trastuzumab-related cardiotoxicity are previous or concurrent use of anthracycline and age greater than 50 years [12,15,16]. Elderly patients (≥70 years), which have been traditionally excluded from clinical trials, are at especially high risk for Trastuzumab related Cardiotoxity. A retrospective study that evaluated patients with 70 years old or more treated with Trastuzumab, showed an incidence of 8.9% in the development of symptomatic congestive heart failure for the metastatic patients cohort [17].

Other risk factors include decreased baseline LVEF, increased body mass index and previous hypertension [14]. A recent study evaluated troponin 1 levels before and after each Trastuzumab cycle in women with early stage or advanced BC. Trastuzumab Cardiac Event, defined as LVEF decrease of 10 units and below 50%, was more commonly seen in patients with elevated levels of troponin 1 (62% versus 5%; $p < 0.001$). Also, LVEF recovery occurred less frequently in patients with elevated troponin 1 (35% versus 100%; $P < 0.001$) [18].

Surveillance for trastuzumab-related cardiotoxicity is largely empirical [19,20]. Cardiac function should be assessed prior to trastuzumab therapy. Clinical Oncologists should determine previous cardiac events and risk factors for each patient. Also, we feel that a 12-lead electrocardiogram (ECG) – looking for possible markers of structural heart disease is recommended. Additionally, a baseline exam to obtain the Left ventricular ejection fraction measurement, using echocardiogram or radionucleotide multiple-gated acquisition (MUGA) scan is also extremely important. Repeat echocardiogram or MUGA every three months of therapy and also at the end of Adjuvant Trastuzumab treatment. For the metastatic patients, we recommend repeating echo or MUGA every 3 months.

Patients with a normal baseline LVEF and no signs or symptoms of heart failure are able to start therapy. Patients with a modestly increased risk for cardiotoxicity (include those with borderline LVEF between 50 and 55 percent, age >50 years and hypertension) should also be considered for treatment with trastuzumab, after careful consideration of the potential harms and benefits. In this group of patients, one should consider the use of non-anthracycline containing trastuzumab schedules [7].

Although the late onset of cardiac dysfunction seems to be uncommon, it is advisable to continue LVEF assessments every 6 months for at least 2 years after completion of treatment [14,16]. In the metastatic setting, the routine assessment is less clearly defined. Nevertheless, we believe that there is no reason not to propose the same schedule as in the adjuvant setting. Some of these patients can become long-term survivors, and cardiac function is an important part of the quality of life [18].