Cancer Treatment Reviews 52 (2017) 1–11

Contents lists available at ScienceDirect

Cancer Treatment Reviews

journal homepage: www.elsevierhealth.com/journals/ctrv

Anti-Tumour Treatment

Escalating and de-escalating treatment in HER2-positive early breast cancer

Heikki Joensuu *

Helsinki University Hospital and University of Helsinki, Helsinki, Finland

ARTICLE INFO

Article history:
Received 22 August 2016
Received in revised form 30 October 2016
Accepted 3 November 2016

Keywords:
Breast cancer
Human epidermal growth factor receptor 2
Trastuzumab

ABSTRACT

The current standard adjuvant systemic treatment of early HER2-positive breast cancer consists of chemotherapy plus 12 months of trastuzumab, with or without endocrine therapy. Several trials have investigated modifications of the standard treatment that are shorter and less resource-demanding (de-escalation) or regimens that aim at dual HER2 inhibition or include longer than 12 months of HER2-targeted treatment (escalation). Seven randomized trials investigate shorter than 12 months of trastuzumab treatment duration. The shorter durations were not statistically inferior to the 1-year duration in the 3 trials with survival results available, but 2 of the trials were small and 1 had a relatively short follow-up time of the patients at the time of reporting. The pathological complete response (pCR) rates were numerically higher in all 9 randomized trials that compared chemotherapy plus dual HER2 inhibition consisting of trastuzumab plus either lapatinib, neratinib, or pertuzumab with chemotherapy plus trastuzumab as neoadjuvant treatments, but the superiority of chemotherapy plus dual HER2-inhibition over chemotherapy plus trastuzumab remains to be demonstrated in the adjuvant setting. One year of adjuvant trastuzumab was as effective as 2 years of trastuzumab in the HERA trial, and was associated with fewer side-effects. Extending 1-year adjuvant trastuzumab treatment with 1 year of neratinib improved disease-free survival in the ExteNET trial, but the patient follow-up times are still short, and no overall survival benefit was reported. Several important trials are expected to report results in the near future and may modify the current standard.

Introduction

Human epidermal growth factor receptor 2 (HER2) is a tyrosine kinase encoded by the *ERBB2* gene, located at 17q12. *ERBB2* amplification leads to overexpression of the HER2 protein [1,2]. HER2-positive breast cancers frequently give rise to distant metastases at visceral sites as compared to luminal A cancers [3,4]. In the era that preceded the modern systemic therapies even small node-negative HER2-positive cancers ⩽2 cm in diameter were associated with a 20–30% risk for distant metastases [5,6]. HER2-positive breast cancers are usually identified with either presence of HER2 protein overexpression in breast tumor tissue at immunohistochemistry or *ERBB2* amplification at *in situ* hybridization. The HER2-status of the primary breast tumor and paired distant metastases are discordant in about 10% of the patients [7,8]. *ERBB2* is amplified in 15–25% of breast carcinomas, the frequency being influenced by the criteria used to define HER2-positivity [9].

Patients with early HER2-positive breast cancer benefit from HER2-targeted systemic therapy. The only exception is patients with small (⩽5 mm) node-negative cancer, when local therapy alone is considered sufficient [10,11]. Patients with HER2-positive cancer that expresses estrogen receptors (ER) and/or progesterone receptors (PgR) are treated with adjuvant endocrine therapy as other patients with steroid hormone receptor-positive breast cancer [10].

This review discusses the current systemic adjuvant and neoadjuvant HER2-targeted treatments for early HER2-positive breast cancer, and the attempts to modify the treatment by either making it shorter, less toxic, and less resource-demanding (de-escalation), or more effective with dual HER2 inhibition or extending the treatment duration (escalation). These 2 strategies are not necessarily mutually exclusive, as dual HER2-inhibition may potentially be integrated in regimens of short duration.

Current standard treatment

The currently recommended standard adjuvant treatment for patients with early HER2-positive breast cancer is chemotherapy

* Address: Helsinki University Hospital and University of Helsinki, Haartmaninkatu 4, P.O.B. 180, FIN-00029 Helsinki, Finland. Fax: +358 9 471 74202.
E-mail address: heikki.joensuu@hus.fi

http://dx.doi.org/10.1016/j.ctrv.2016.11.002
0305-7372/

plus trastuzumab administered for 1 year. Chemotherapy consists usually of a few cycles of an anthracycline-containing regimen followed by a taxane, the latter given concurrently with trastuzumab. Docetaxel, carboplatin, and trastuzumab (TCH) is an option, particularly for patients who are unsuitable for anthracycline-containing treatment [10,12]. Even patients with small HER2-positive cancer benefit from adjuvant trastuzumab [13], but anthracyclines may not be needed when treating node-negative cancer ⩽1 cm in diameter, as such patients have a high disease-free survival (DFS) rate when treated with 1 year of trastuzumab plus paclitaxel [14] or 4 cycles of docetaxel and cyclophosphamide [15].

Adjuvant trastuzumab was first investigated in 4 large randomized trials as the treatment of early HER2-positive breast cancer, the National Surgical Adjuvant Breast and Bowel Project (NSABP) trial B-31, the North Central Cancer Treatment Group (NCCTG) trial N9831, HERA, and the Breast Cancer International Research Group (BCIRG) trial 006 [16,17,12]. The same trastuzumab dose (2 mg/week) and the same duration (12 months) were selected for evaluation in all 4 trials. The 12-month duration was studied also in 2 smaller randomized adjuvant trials, the NOAH [18] and the PACS 04 [19] trials. The choice of the 12-month duration for study was arbitrary [20], and no clinical or preclinical evidence to support this duration existed. The Food and Drug Administration (FDA) approved adjuvant trastuzumab in 2006, as there was compelling evidence for efficacy and the safety profile was favorable. In the absence of data from other durations than the 12-month duration, the 1-year duration became the standard.

In a Cochrane Breast Cancer Group literature search that included 8 randomized controlled adjuvant trials and 11,991 patients, the combined hazard ratios (HRs) for DFS and overall survival (OS) favored very significantly the trastuzumab-containing regimens over the same chemotherapy without trastuzumab. There were 40% fewer cancer recurrences in the groups treated with trastuzumab (HR 0.60, 95% confidence interval [CI] 0.51–0.71) and 34% fewer deaths (HR 0.66, 95% CI 0.57–0.77) [21]. The favorable effect of adjuvant trastuzumab on survival appears durable. In the planned joint analysis of the B-31 and the N9831 trials based on a median follow-up time of 8.4 years of the patients, adding trastuzumab to chemotherapy improved the 10-year OS rate from 75% to 84% (a relative improvement of 37% as compared with the chemotherapy only group) and the 10-year DFS rate from 62% to 74% (a relative improvement of 40%) [22].

Trastuzumab is generally well tolerated, but periodical monitoring of the cardiac left ventricular ejection fraction (LVEF) is considered mandatory as trastuzumab increases the risk of congestive heart failure (CHF). In a meta-analysis the absolute overall risk for high-grade CHF among 18,111 patients who participated in 6 randomized controlled adjuvant trials evaluating trastuzumab was 1.4%, and the relative risk as compared with the control groups 3.2 [23]. Patients treated with adjuvant trastuzumab for 2 years had a higher risk for cardiac adverse effects than those treated for 1 year [24], whereas a 9-week course of trastuzumab was associated with no detectable risk [23]. Another overview analysis found an increased risk for severe heart failure in patients treated with trastuzumab-based versus non-trastuzumab-based regimens of 2.5% and 0.4%, respectively (a relative risk of 5.11) [21]. Almost all cardiac failures are detected within the first 2 years since starting adjuvant trastuzumab. In one study, follow-up for a median of 9.2 years revealed only 2 additional diagnoses of CHF among 1046 patients after the first 3 years of follow-up, indicating that late onset of trastuzumab-related cardiac failure is rare [25]. The LVEF recovers in most patients who develop heart failure after trastuzumab discontinuation and initiation of therapy for heart failure [24–26]. A low LVEF, hypertension medication, coronary artery disease, and age have been identified as risk factors for trastuzumab-related cardiac failure [25–27]. Yet, as geriatric patients were underrepresented in the major adjuvant trials [28] and those with cardiac risk factors were excluded, the risk may be higher in population-based studies [29]. In a cohort study among breast cancer patients aged >65 and with full Medicare coverage, the rate of CHF was 29.4% among trastuzumab users as compared to 18.9% among the non-users [27].

Trastuzumab chemotherapy partners

Administration of some chemotherapy agents concomitantly with trastuzumab likely improves efficacy substantially. Preclinical studies suggest that docetaxel, vinorelbine, cyclophosphamide, and platinum salts are synergistic with trastuzumab [30,31]. The combination of docetaxel plus trastuzumab has been compared to single-agent trastuzumab in 2 randomized trials in advanced HER2-positive breast cancer [32,33]. In these 2 trials, the patients allocated to docetaxel plus trastuzumab had a median time to disease progression of 14.6 and 9.4 months compared to only 3.7 and 3.4 months, respectively, in the groups allocated to single-agent trastuzumab, suggesting that adding concomitant docetaxel to trastuzumab approximately triples the time to progression compared to trastuzumab alone. Furthermore, the only randomized trial (N9831) that compared concomitant administration of adjuvant trastuzumab with chemotherapy (weekly paclitaxel) to sequential administration found the 5-year DFS rate to favor concomitant administration (84.4% vs. 80.1%, respectively) [34]. These data suggest that the chemotherapy partners given concomitantly with trastuzumab are important for the overall regimen efficacy. With the exception of the B-31 and the N9831 trials that shared 2 treatment arms [16], the companion chemotherapy agents varied in the randomized trials that evaluated adjuvant trastuzumab, and in the HERA and the PACS 04 trials all trastuzumab was administered only after chemotherapy completion [17,19].

Randomized de-escalation trials

Seven randomized trials ask the question whether comparable efficacy to 1-year adjuvant trastuzumab can be achieved with a shorter regimen, but with fewer side-effects (Table 1). In 4 of these trials all trastuzumab is administered concomitantly with chemotherapy in the experimental arm in an attempt to exploit drug synergism (FinHer, E2198, SOLD, and Short-HER trials), and 3 trials compare 6-month to 12-month duration of trastuzumab (the Hellenic trial, PHARE, and PERSEPHONE) [35–42].

FinHer was the first randomized trial to evaluate a shorter than the 12-month duration of adjuvant trastuzumab, and may be considered as the first de-escalation trial. FinHer accrued 1010 patients with early breast cancer from 17 centers in Finland in October 2000 to September 2003. The patients were assigned to either 3 3-weekly cycles of docetaxel or weekly vinorelbine, each followed by 3 3-weekly cycles of FEC. The 232 patients with HER2-positive disease had a second randomization to weekly trastuzumab, given upfront and concomitantly with either docetaxel or vinorelbine, or to observation [35]. The selection of docetaxel and vinorelbine as the companion agents with trastuzumab was based on preclinical data that suggested drug synergism [30]. The duration of 9 weeks of HER2-targeted therapy resulted from the duration of 3 3-weekly given chemotherapy cycles. The Finnish Breast Cancer Group sponsored the trial, and funding for trastuzumab was obtained from the government budget of Finland. Somewhat unexpectedly, the patients treated with 9-week trastuzumab plus docetaxel or vinorelbine had a comparable hazard ratio for cancer recurrence (0.42, 95% CI 0.21–0.83) as was achieved in the B-31, N9831, and HERA trials with 1-year duration of trastuzumab [35], suggesting that the brief administration of trastuzumab with