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REVIEW ARTICLE

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Neratinib in adjuvant treatment of patients with HER2-positive breast cancer — less is more?

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ABSTRACT

Neratinib is a new small molecule aimed at HER2 receptor. It has recently been approved in the United States of America and Europe for adjuvant treatment of patients with early, HER2-positive breast cancer, who underwent surgical resection followed by at least one year of adjuvant trastuzumab treatment. Despite initial enthusiasm, several factors limit the implementation of neratinib in clinical practice. These include: modest reduction of recurrence rate; limited data regarding the effect on overall survival; and a significant rate of adverse events. Thus, neratinib should be considered mainly in patients with high-risk HER2-positive breast cancer, because its clinical benefit might outweigh the side effects in this population. In the following article, we discuss the controversies regarding the pivotal phase III trial that eventually led to neratinib approval.

Key words: neratinib, breast cancer, HER2

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Introduction

Recent years have brought significant improvement in systemic treatment of breast cancer. Recognition of the biological mechanisms responsible for breast cancer development and growth have led to the introduction of personalised treatment that bases on the immunological phenotype of cancer cells. Systemic treatment armamentarium for breast cancer in the USA includes over 30 agents nearly half of which are molecularly targeted drugs. Neratinib is one of the most recent additions to this list and acts as a molecularly targeted drug [1].

Phase II clinical trials

Neratinib is a small molecule oral tyrosine kinase inhibitor. It irreversibly blocks human epidermal growth factor receptor 2 (ERBB2, HER2) and epidermal growth factor receptor (EGFR) [2]. The mechanism of action relies on the suppression of ErbB and autophosphorylation of EGFR family receptor proteins, leading to the impairment of cell proliferation. In a phase II trial published in 2010, neratinib was evaluated in patients with metastatic, HER2-positive breast cancer. The patients were divided into two cohorts — the first included patients with a confirmed progression during trastuzumab treatment, and the second only patients naïve to trastuzumab. Neratinib was used at a dose of 240 mg per day. The primary end point was the rate of progression-free survival (PFS) after 16 weeks of treatment. The rate of PFS was 56% in the first cohort and 78% in the second cohort, with a median PFS of 22.3 and 39.6 weeks, respectively. The response rate was 24% in patients who progressed on trastuzumab and 56% in trastuzumab-naïve patients. The most common treatment-related adverse events were diarrhoea, nausea, vomiting, and fatigue. Diarrhoea usually occurred in the first week of treatment and was present in 93% of patients, with grade 3 and 4 intensity (according to National Cancer Institute Common Terminology Criteria for Adverse Events v.3.0, CTCAE) in 21% of patients. Grade 3 and 4 diarrhoea was more prevalent in the cohort of patients with prior trastuzumab exposure

(30%) compared to the cohort of trastuzumab-naïve patients (13%). Dose reduction was required in nearly one-third of patients in cohort one (29%), in contrast to only 4% of patients who needed dose reductions in cohort two [3]. The next phase II trial, the results of which were published three years later, aimed at proving non-inferiority of neratinib monotherapy to a combination of lapatinib and capecitabine in patients with locally advanced or metastatic HER2-positive breast cancer after prior trastuzumab treatment. Patients in the experimental arm received neratinib 240 mg per day continuously (n = 117), and patients in the control arm received lapatinib 1250 mg per day continuously and capecitabine 2000 mg/m^2 daily on days 1–14 of every 21 day cycle (n = 116). The trial failed to show non-inferiority of neratinib. Median PFS in patients receiving neratinib was 4.5 months versus 6.8 months in patients receiving lapatinib and capecitabine, with a median overall survival (OS) of 19.7 and 23.6 months, respectively. The response rate was lower in the experimental arm (29%) compared to the control arm (41%) (p = 0.067), as was the rate of clinical benefit (44% *vs.* 64%, respectively) (p = 0.003). Patients receiving neratinib experienced more diarrhoea (85%) compared to patients receiving lapatinib and capecitabine (68%) (p = 0.002) [4]. Several other phase I/II trials evaluated neratinib combined with different cytotoxic agents (vinorelbine, capecitabine, and paclitaxel) in the treatment of patients with breast cancer, with a modest signs of activity [5–7].

Phase III clinical trial

Results of a prospective, randomised, multicentre, double-blinded, placebo-controlled trial evaluating neratinib in adjuvant treatment of patients with HER2-positive breast cancer, who underwent surgery followed by at least one-year of trastuzumab treatment, were published in 2016 in „The Lancet Oncology". The trial included patients from 495 oncological centres from all continents. Initially, the trial included patients over 18 years old with stage I–III HER2 breast cancer, who finished 12-months of adjuvant trastuzumab treatment within the last two years. Patients whose tumours expressed oestrogen receptors were recommended to receive endocrine therapy simultaneously. Hormonal receptor expression was evaluated locally and was not verified by a central laboratory. No homogenous method of receptor evaluation was required. Inclusion criteria included only typical factors: adequate performance status (ECOG 0–1); no clinical or laboratory contraindications arising from liver, kidneys, or heart; no diagnosis of mental diseases; and no difficulties with oral ingestion. Neratinib was administered at a daily dose of 240 mg continuously for 12 months. Dose reductions or interruptions for no longer than three weeks were allowed. No diarrhoea prophylaxis was included; treatment was initiated if necessary. Besides routine clinical and radiological assessment, the trial included quality-of-life evaluation, using EuroQoL Five Dimensions (EQ5D) and Functional Assessment of Cancer Therapy-Breast (FACT-B) questionnaires. Quality of life evaluation was undertaken every three months. The primary end-point was invasive disease-free survival (iDFS) assessed 24 months after randomisation. Secondary end-points were: DFS including incidence of preinvasive breast cancer, distant recurrence-free survival, cumulated incidence of central nervous metastases incidence, overall survival, and treatment safety.

In February 2010 the protocol was modified, narrowing the inclusion criteria to patients with stage II and III disease and to those who finished trastuzumab therapy within a year. The amendment was justified by the results of two other published clinical trials (BCIRG 006), which showed excellent survival parameters of patients with HER2 overexpressed breast cancer without involvement of local lymph nodes, who received adjuvant trastuzumab. Additionally, most of the recurrences occurred within one year of completing adjuvant treatment [8]. In October 2011 subsequent amendments were implemented. The trial finished recruitment after only 2842 patients from 3850 initially planned, and the observation period was limited to two years instead of a previously accounted five years. Those amendments, as described with published results, were due to the sponsor's doubts regarding safety [9]. Moreover, a previous sponsor withdrew financial support for the trial, which was continued by a small pharmaceutical company with limited experience in oncology.

The next amendment was implemented in January 2014. The decision revived some of the initial study assumptions and prolonged the period of observation, again, to five years, with an additional efficiency analysis in the whole study population after 24 months from randomisation. The aforementioned analysis was undertaken in June 2014. In the neratinib arm, there were 70 events of invasive breast cancer in comparison to 109 events in the placebo arm (HR 0.67; 95% CI 0.50–0.91; p = 0.0091). The difference was even more clear in a subgroup of patients with positive hormone receptors (HR 0.51; 95% CI 0.53–0.77; p = 0.0013). No difference in iDFS was seen in patients without expression of hormonal receptors. There were no differences regarding the metastasis-free survival (HR 0.75; 95% CI 0.53–1.04; p = 0.089) or the distant recurrence-free survival (HR 0.71; 95% CI 0.50–1.0; p = 0.054). The cumulative incidence of central nervous system metastases was similar in both arms (0.91% [95% CI 0.49–1.59] and 1.25% [95% CI 0.75–1.99]; p = 0.44). Quality of life assessment showed impaired scores in the neratinib group

during the first month of treatment, with a subsequent diminishment of difference between both arms.

The restitution of a five-year period of observation required renewal of informed consent, which was obtained from 2117 patients (74.4% of the primary group). Data regarding patients who refused re-consent were censored at the date of last control. Results from the five-year observation were published in „The Lancet Oncology" [10] and were comparable to the results published after the 24-month analysis. The median treatment time was 353 days in the neratinib group and 360 days in the placebo group. Among patients with hormonal-receptor-positive cancer, 93% of patients in the experimental arm and 94% of patients in the placebo arm received simultaneous hormonal treatment, but at the time of final analysis only 52% and 47%, respectively, continued endocrine treatment. The difference between arms might be attributed to the higher rate of disease recurrence in the control arm, which forced hormonal therapy withdrawal. Long-term analysis showed a significantly lower rate of invasive breast cancer in the neratinib group compared to the control group (116 and 163 events, respectively; HR 0.73; 95% CI 0.57–0.92; p = 0.0083). The rate of five-year recurrence-free survival was 90.2% (95% CI 88.3–91.8) in the neratinib arm and 87.7% (95% CI 85.7–89.4) in the placebo arm. There were no significant differences between rates and medians of distant recurrence-free survival as well as cumulative five-year risk of central nervous system metastasis development. Again, the greatest difference in recurrence-free survival was seen in a sub-group of patients with a cancer expressing hormonal receptors (HR 0.60; 95% CI 0.43–0.83; p = 0.063), and no difference was seen in patients without receptor expression (HR 0.95; 95% CI 0.66–1.35). No long-term toxicities attributed to neratinib were observed, including rates of cardio-vascular diseases and rates of secondary malignancies. During the five-year observation, there were 121 incidences of death, 102 of which can be attributed to cancer and 19 to other causes. The results regarding overall survival have not been published yet because such analysis is planned for the third quarter of 2019 [10].

Adverse events

The most common adverse event during neratinib treatment is diarrhoea, with all grade incidents present in over 70% of patients (33% grade 2, 40% grade 3, and less than 1% grade 4 diarrhoea). Treatment emergent adverse events were responsible for a 28% rate of treatment withdrawal in the neratinib group (compared to 2% in the placebo group) and a 31% rate of dose adjustment (compared to only 2% patients in the placebo group). Serious adverse events were reported in 7% and 6% of patients, respectively, with the most common being diarrhoea (22 *vs*. one event/s), vomiting (12 *vs*. one event/s) and dehydration (nine *vs*. one event/s). Grade 2, 3, and 4 diarrhoea usually emerged during the first week of treatment, with an increased risk during the subsequent few weeks. The presented trial did not include diarrhoea prophylaxis. However, conclusions arising from the trial suggest that this kind of prophylaxis should be encouraged in patients receiving neratinib. The prophylaxis should be initiated concurrently with neratinib and continued for the first two treatment cycles and as clinically indicated thereafter [10, 11]. Quality of life assessment is an essential factor during evaluation of novel drugs, especially when applied as part of adjuvant treatment. Results regarding quality of life in the ExteNet trial were published as a conference paper during the European Society for Medical Oncology Congress in 2017. The presented results included evaluation of health-related quality of life (HRQoL) assessment with two properly validated questionnaires: EuroQol Five Dimensions (EQ5D) and Functional Assessment of Cancer Therapy-Breast (FACT-B). The assessment was undertaken every three months for 12 months. Similar patterns of HRQoL changes were detected in both FACT-B and EQ-5D questionnaires: the quality of life scores in the neratinib group worsened in the first month of treatment but improved thereafter [11].

Discussion

Neratinib used as part of adjuvant treatment in patients with early-stage HER2-positive breast cancer improves invasive disease-free survival and non-invasive disease-free survival, especially in patients with tumours expressing hormonal receptors. No improvement with neratinib was seen regarding distant metastasis-free survival and rate of central nervous system metastasis incidence. Additionally, we currently lack data regarding survival parameters. Better results obtained with neratinib in hormonal-positive patients might be explained by an interaction of HER2 and oestrogen receptors. Inhibition of the former leads to an overexpression of the latter, sensitising cancer cells to hormonal treatment. It should be emphasised that improved effectiveness in the hormonal-positive population has not been observed in a trial with other HER2 inhibitors: trastuzumab, pertuzumab, or lapatinib. A possible explanation might be that neratinib itself can interact with oestrogen receptors. However, as the central assessment evaluated only HER2 receptor status and not hormonal receptor expression, the differences between multiple local standards might bias correct interpretation of data. Several controversies arise due to the few protocol amendments undertaken during the trial and due to the change of sponsorship. The decision regarding limitation of the number of participants correlated

with a primary analysis of a different small molecule HER2 inhibitor — lapatinib — used as a monotherapy in adjuvant treatment of HER2-positive breast cancer. The inferiority of lapatinib compared to trastuzumab led to an early trial suspension, and patients receiving lapatinib were offered to continue their treatment with trastuzumab [12]. Because the neratinib trial was modified at the same time that the lapatinib trial results were made available, the sponsor might have limited recruitment only to reduce costs due to a high risk of obtaining negative results. Despite the lack of overall survival data, on 17 June 2017 the Food and Drug Administration (FDA) approved neratinib as an adjuvant treatment in adult early-stage HER-2 positive breast cancer patients who received at least 12 months of trastuzumab treatment [13]. Initially, in February 2018 the European Committee for Medicinal Products for Human Use (CHMP) did not recommended registration of neratinib due to uncertainties whether the clinical benefit outweighs the increased toxicity [14]. However, four months later, on 28 June 2018 the CHMP revised its position and recommended registration of neratinib, but only in the population of patients with HER2-positive and hormone receptor-positive tumours. Since then, neratinib can be considered as an option for extended adjuvant treatment of HER2-positive and hormonal receptor-positive early-stage breast cancer [13].

The monthly cost of neratinib therapy in the USA is estimated at about 10,000 dollars, and, considering a standard 12-month regimen, a single neratinib treatment requires expenditure of 120,000 dollars. Unfortunately, toxicities related to neratinib occur commonly, add a substantial burden, require intensive prophylaxis, and can impair quality of life (at least temporarily during the first months of treatment). Valuable insights might come with the data regarding survival parameters, but they will not be available until late 2019. Additionally, quality of life analysis of neratinib has been published only as a conference paper, which limits the ability to draw proper conclusions.

Conclusions

Recent advances in systemic therapy of solid tumours are limited mostly to targeted therapies and drugs aimed at the immune system (mostly immune checkpoint inhibitors). The last cytotoxic drug for breast cancer was registered in the USA in 2012. Since then, all drugs registered were molecularly targeted therapies. Trials evaluating immune checkpoint inhibitors in triple-negative breast cancer are underway. Strong pression from millions of breast cancer patients around the globe, as well as technological development, has led to the introduction of novel and promising therapies. The exponentially growing body of evidence regarding cancer genetics, supported by more precise technological advancements, has shortened the cycle of drug development and allows rapid introduction of novel compounds to the market.

Still, it should be remembered that the daily practicing oncologist, who meets patients and their needs, is the one responsible for the final recommendation of certain treatment for a certain patient. Knowledge about the full process the development of a novel drug offers a valuable insight into its clinical utility and supports precise and accurate therapeutic decisions [15].

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