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Anti-Tumour Treatment

Trastuzumab in small tumours and in elderly women

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ABSTRACT

Results of trials assessing the role of trastuzumab in the adjuvant setting in early breast cancer have brought a new standard of treatment to clinical practice. Nevertheless, some groups of patients are underrepresented in these trials and thus therapy should be planned based on incomplete information or lack of solid data. Two of these groups are high-risk HER2+ small tumours (<1 cm) and elderly patients. In this review we aimed at addressing the most relevant data about these two populations underrepresented in clinical trials. HER2 overexpression or amplification confers a bad prognosis in patients with small breast tumours. Mammographic screening is increasing the early diagnosis. Taking into account that specific targeted adjuvant treatment can avoid relapses in 50% of HER2-positive patients, about 2 to 7% of relapses from small tumours could be avoided with the use of this treatment. Randomized and non-randomized trials support the idea that adjuvant therapies could improve clinical outcomes of ⩽1 cm tumours. Adding a HER2-targeted treatment to chemotherapy may improve efficacy. Some recent data in the neo-adjuvant context suggest that, in some patients, aggressive chemotherapy treatment could be properly substituted by HER2-targeted therapy. In elderly women with HER2+ breast cancer, trastuzumab should be considered for adjuvant-treatment, particularly in those at higher risk of relapse, lack of extra risk factors for trastuzumab-associated cardiotoxicity, and having a prolonged estimated life expectancy. In addition to traditional anthracycline–based combinations commonly used in younger women, other options are the use of sequential chemotherapy, non-anthracycline containing regimes plus anti-HER2 therapies, combinations with hormonotherapy, or even anti-HER2 agents alone.

Introduction

Clinical trials are an important tool to explore the benefit of a new compound or to verify the effectiveness of a therapy in new settings. Positive or negative results of a well-designed and appropriately-powered trial are considered representative of the effect of a study drug on the whole population. However, trial results are not always reproducible in a non-selected population. Exclusion and inclusion criteria defined in every clinical study may frequently favour the accrual of a homogenous tumour and/or subtype or category, and prevent an adequate recruitment of patients from a specific subgroup. If selection of patients is not well-balanced, results of the trial might be biased or not reflect the real effect of the study drug in some subgroups. Meanwhile, clinicians must wrestle with practical day-to-day questions that remain unanswered.

Human epidermal growth factor receptor 2 (HER2) is both a prognostic and predictive factor in breast cancer, and it is amplified in 15 to 20% of early breast tumours. Its value as a strong predictive factor for targeted therapy has been demonstrated in numerous clinical trials in the last decade since a pivotal trial publication.[1] Trastuzumab is a monoclonal antibody that targets the extracellular domain of HER2, and, in combination with chemotherapy, improves clinical outcomes, including overall survival, in the metastatic setting. Importantly, the results of five randomized trials of adjuvant trastuzumab have demonstrated an improved survival and a 50% relative risk reduction in recurrence with the addition of trastuzumab during or after adjuvant chemotherapy,[2–5] showing a similar efficacy in node-positive and node-negative patients.

Results of trials assessing the role of trastuzumab in the adjuvant setting in early breast cancer have brought a new standard of treatment to clinical practice. Today, adjuvant or neoadjuvant trastuzumab should be considered as an option in the management of the vast majority of HER2+ early breast cancer. Nevertheless, in

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clinical practice, two groups of patients are underrepresented or excluded in these trials and thus therapy should be planned based on incomplete information or lack of solid data. These two subgroups in HER2+ early breast cancer trials are HER2+ small tumours and elderly patients. These two groups are commonly excluded from clinical trials since adjuvant trials require a certain number of events and therefore depend on higher risk subsets, and safety concerns precluded participation of the elderly in the pivotal studies. Diagnosis of breast cancer with a tumour size <1 cm is gradually increasing in clinical practice. Mammographic screening has led to the frequent diagnosis of smaller, node-negative tumours.[6–10] It has long been appreciated that small (<1 cm) node-negative breast cancer carry a more favourable prognosis. Nevertheless, the identification of more accurate prognostic factors led to the hypothesis that small tumours with high-risk features are likely to warrant adjuvant chemotherapy, whereas higher stage tumours with favourable biologic features may not.[11] Adjuvant systemic therapy reduces the risk of recurrence and improves survival even in node-negative breast cancer patients; however the absolute benefit decreases as the risk of recurrence lessens.[12] Trials of adjuvant trastuzumab concluded that addition of trastuzumab during and/or after chemotherapy improved survival.[2–5,13]

Four of these studies included node-negative breast cancer patients but these were a minority and, although the efficacy was similar, the absolute benefits were inferior in the node-negative subgroup. Because of the implications of a long-duration adjuvant treatment, trastuzumab costs, and the risk of cardiotoxicity, establishing recommendations for the use of trastuzumab in HER2-overexpressed, small, node-negative breast cancer would aid the clinicians.

The second classically underrepresented group in clinical trials includes elderly patients. About half of the women diagnosed with a breast cancer every year are 65 years or older. Despite this important proportion of elder breast cancer patients, available data suggest that treatment offered to these patients in clinical practice is often suboptimal[14]. Prevalence of HER-2 positive tumours in women aged >70 years varies in different case series from 7%[15] to 20%.[15–17] Retrospective series show that benefits and safety of trastuzumab appear to be conserved in patients aged more than 60[18] and 70 years.[19] Since the incidence of cardiac events tended to increase with age in the trastuzumab trials, its administration must be carefully considered in elderly patients, and monitoring of cardiac function is strongly recommended. Though substantial evidence exists to support the addition of trastuzumab to adjuvant or neoadjuvant chemotherapy in the treatment of HER2-overexpressed breast cancer, accrual of older patients has been poor in these trials.[20,21] There is no consistent evidence on the risk–benefit ratio of anti-HER2 therapy in elderly patients with varying health status and co-morbidity. In the absence of sufficient data, the decision to add or not trastuzumab to the adjuvant or neoadjuvant strategy in older adults remains a point of controversy and is subject to practitioner bias.

In this review we aimed at addressing the most relevant data about the two forgotten subgroups in the trials of trastuzumab in HER2+ early breast cancer: the small high-risk tumours and the management of elder patients.

HER2 overexpression as an adverse prognostic factor in pT1a,b N0 breast cancer

Taking into account the predictive value of HER2 and the good results of trastuzumab in breast cancer patients, the question that has been addressed is whether HER2-positive, small (<1 cm) node-negative tumours have a poorer prognosis than other pT1a,b cancers and, if so, whether they require additional adjuvant systemic therapy including anti-HER2 treatment. The absence of clinical trials that test the value of adjuvant trastuzumab in pT1a,b tumours leads to a clinical dilemma. Even more, the wide implementation of mammographic screening has led to the detection of primary tumours in earlier stages than a few years ago; so this is a recently posed question with a high clinical relevance and for which no standard of care is currently available. Latest editions of prestigious guidelines such as St. Gallen's and NCCN guidelines, recommend adjuvant therapy for T1bN0 patients, particularly for negative hormone receptors tumours.[22,23] In consequence some patients with subcentimetre tumours receive a variety of chemotherapy treatments with or without trastuzumab, whereas other patients do not receive any therapy at all.

Retrospective studies of outcomes in patients with pT1a,b cancer treated with locoregional therapies alone have shown a 10-year relapse-free survival (RFS) of more than 90%[24,25] which justifies the recommendation of no systemic adjuvant therapy for these patients. However, other factors such as lymphovascular invasion or histological grade can affect prognosis. Some of the more informative data on this matter come from the British Columbia dataset, that includes 430 pT1a,b N0 patients not receiving adjuvant therapy. With a median follow-up of 10.4 years, RFS decreased over time (10-year disease-free survival [DFS] 82%).[26] The recognition that subsets of small tumours generally considered to be low-risk have a different prognosis led to address whether HER2 overexpression is of prognostic value. In order to define the risk of recurrence of small, HER2-positive breast cancers and, by inference, to recommend adjuvant treatment with chemotherapy and/or trastuzumab, multiple investigators have conducted retrospective studies to characterize the risk of recurrence among tumours <1 cm that overexpress HER2 (Table 1). Although the adjuvant treatment received by patients in these retrospective series is not homogenous, we shall review them to try to answer the essential question: Should <1-cm breast tumours be treated?

In an extension of the British Columbia series of 2026 node-negative patients, 328 (27%) had tumours less than 1 cm. Further analyses including HER2 expression (that was positive in 10.6% of the node-negative cohort) showed that clinical outcomes were significantly worse for HER2-positive cases (10-year RFS 65.9% vs. 75.5%, $p \leqslant 0.01$).[17] HER2 was an independent poor prognostic factor for RFS at 10 years (OR = 1.71). The number of HER2+ tumours of 1 cms or less was small but there was a trend for a worse outcome in T1b tumors".

Rakkhit reviewed a large cohort of 1796 patients with stage T1a,bN0M0 breast cancers diagnosed between 1973 and 2003. 123 of them (9%) were HER2-positive. At a median follow-up of 74 months, HER2-positive patients had a significantly worse RFS, with a 61.7% probability of relapse-free survival at 10 years (HR 5.19) and a 80.1% probability of distant relapse-free survival at 10 years (DRFS) (HR 4.66) compared with HER2-negative patients.[27]

Joensuu et al.[28] identified 852 pT1a,b patients, with HER2 overexpression being present in 12% (69) of them. Three hundred and thirteen patients (36.7%) had tumours smaller than 1 cm. Distant disease-free survival (DDFS) in HER2 positive or negative cases could not be established for patients with tumours of a low grade due to the small number of patients. However, for patients with tumours with histological grade II (277 patients, 44%) or III (101 patients, 16%), 9-year DDFS was 67% vs. 92%. HER2 overexpression was identified as an adverse prognostic factor in multivariate analysis (HR 2.56, $p = 0.04$). This trial supports the idea that the outcome of such HER2-positive tumours even if smaller than 1 cm, is sufficiently bad to justify the prescription of adjuvant systemic therapy.

An important retrospective review from M.D. Anderson Cancer Center of 965 patients with T1a,b N0 breast cancers has been reported.[29] No patient received adjuvant systemic therapy. All