

Choice of chemotherapy regimen for early HER2-positive breast cancer in elderly patients

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Over the last four decades demographic transition has increased significantly the number of elderly individuals in industrialized societies. For oncologists, this has translated into an increasing number of elderly patients in daily practice. Today, in certain countries, up to 50% of new breast cancer cases are diagnosed in women 65 or older (1). Though recent data suggests that this is still not the case in China, with mean patient age standing currently at 49 (*vs.* 61 in the USA), it is likely to become the case over the next decades as demographic transition unfolds and life expectancy increases (2).

Treating elderly women with early breast cancer is a significant challenge. Elderly women have specific clinical needs brought about by limited life-expectancy, functional decline, organ dysfunction and comorbidity. These particularities are often reflected in their management preferences and personal goals (3). Furthermore, considering the important impact of cultural, societal and economic issues on the aging process, significant differences may exist between countries (4). Therapeutic decision-making is further complicated by the limited nature of available evidence on the efficacy and safety of some the most commonly used therapeutic agents and regimens in elderly patients. Available data suggests that, though the prognosis of breast cancer has improved in elderly patients, the magnitude of the improvement is smaller than that of younger women (5). This situation is caused by multiple factors, including: (I) low participation rates of elderly

patients in clinical trials; (II) lack of elderly-specific endpoints in most registration trials; (III) reduced adherence to treatment guidelines; (IV) use of suboptimal treatment regimens (6-8). Recent data suggests that, while in adjuvant setting studies elderly participation has improved, it has worsened in other settings (9). The comparatively limited availability of data on how to manage early HER2-positive breast cancer is a good example of this wider reality (10).

Trastuzumab is the first and most important agent in the anti-HER2 class and remains a critical component of treatment, in combination with chemotherapy, for early breast cancer despite recent attempts of integrating dual blockade in this setting (11-13). No elderly specific adjuvant trials testing chemotherapy and anti-HER2 therapy have been published so far and one attempted meta-analysis used a 60-year age cut-off due to the low number of patients, compromising the clinical significance of its results (14). In this scenario, alternative sources of data, such as case series, retrospective studies and observational comparative-effectiveness studies must be relied upon to ground decision-making.

One such study was recently published by Reeder-Hayes *et al.*, investigating the comparative efficacy of ACTH *vs.* TCH as adjuvant therapy in patients older than 65 years (15). Using data from the SEER-MEDICARE database, the authors identified 1,077 patients >65 years older receiving adjuvant therapy with either of two regimens of chemotherapy (TCH or ACTH), and evaluated

multiple end-points, including efficacy, toxicity and choice of chemotherapy regimen over time (15). ACTH and TCH were first tested in the BCIRG-0006 study, and though the study was never designed to compare the 2 chemotherapy backbones, results suggest that the former may be slightly more effective while the latter induces less cardiac toxicity (16).

Surprisingly, the efficacy results of this study for the entire study population suggest a slightly non-significant advantage in terms of 5-year survival of TCH over ACTH: 93% *vs.* 88% [hazard ratio (HR), 1.41; 95% CI, 0.94–2.11]. The ACTH cohort had a higher number of higher risk patients (higher stage, more ER-negative tumours, higher nuclear grade) and a lower rate of trastuzumab treatment completion (77% *vs.* 88%). To evaluate whether higher risk of relapse justified the difference in outcomes, the authors conducted a further analysis in a reduced population, matched exactly for all known risk of relapse-defining characteristics, with similar results for both outcomes and treatment completion. In order to explore the possibility of treatment completion rates being the cause of reduced efficacy, a further analysis was conducted in patients having completed therapy, and this analysis also showed slightly non-significant superior outcomes for the TCH regimen. Considering the nature of this study and the high likelihood of confounding factors, these results cannot be taken as a definitive on the relative efficacy of these two regimens. They suggest, however, that both ensure good outcomes. The overall survival results of this study closely resemble the 5-year overall survival results of BCIRG-006—93% in the former *vs.* 91% in the latter for TCH and 88% *vs.* 92% for ACTH (16), which suggests elderly patients benefit from adjuvant treatment to an extent that is equal or very close to that of other patients.

Toxicity data for the entire population suggest that ACTH is more toxic than TCH with higher rates of neutropenia (57% *vs.* 45%) and heart failure (7.2% *vs.* 3.9%), despite the fact patients receiving ACTH were relatively younger and had less comorbidities. Also notable is that the TCH group experienced a higher rate of dehydration (36% *vs.* 24%). Unfortunately, this study does not report on the incidence of diarrhoea during treatment, a likely cause of dehydration, especially in older populations. In BCIRG-006 the rates of diarrhoea were comparable in both regimens (5.7% with ACTH and 5.4% TCH) (16). No significant difference in terms of toxicity was found between the matched cohorts. Likewise, patients receiving both regimens seem to be at the same risk for admission

and emergency room use. This is particularly critical data as hospital admission carries important risks in elderly patients, including long term disability (17). An important limitation of this study, besides its methodology, is the fact it does not address patient functionality as well as other geriatric parameters. This is, however, an issue shared by most retrospective and prospective studies today (7).

Interestingly, the study also revealed a progressive decline in anthracycline (ATCH) use in recent years (88% in 2005 *vs.* 15% in 2011). Though this study cannot explain this trend, it is likely connected to a perception that TCH is less toxic, an assertion the results presented do not entirely support. It is important to note, however, that studies conducted on cardiac toxicity related to trastuzumab therapy have shown that age and anthracycline use are very important risk factors (18), data that reasonably justifies the choice of non-anthracycline chemotherapy backbone, particularly in elderly patients or patients at a high cardiac risk. This is particularly relevant considering that “real-life” elderly patients have far more cardiac comorbidities than the population participating in registration trials, which is generally a younger and healthier one (7). *Table 1* summarizes the participation of elderly patients in adjuvant anti-HER2 drug trials.

Data on the “real-life” use of trastuzumab in the adjuvant setting is sparse, and this study is the sole one to focus on the chemotherapy regimen rather than on trastuzumab itself. The largest cohort published so far, with 1,014 patients suggest similar improvement in outcomes, but a higher risk of treatment discontinuation (8% in <65 years and 13% ≥75 years). Elderly patient also received trastuzumab monotherapy more often (5% in <65 years and 9% ≥75 years) and are at a higher risk of not receiving trastuzumab at all (23,24). Other smaller studies report similar findings (25). Studies conducted in the advanced setting suggest that, like for their younger counterparts, chemotherapy is an important component of anti-HER2 treatment (26).

Thus, existing data, though suboptimal, suggests that trastuzumab is as effective elderly patients as in younger, should not be foregone on the basis of age alone and can be relatively safely combined with chemotherapy. Toxicity is, however, a significant concern and is likely more intense in elderly patients, regardless of regimen used (3). Additionally, it is important to note that, according to international guidelines, elderly patients should be treated within the context of comprehensive geriatric assessment (CGA) (27). The choice for TCH over ACTH is likely justifiable for

Table 1 Elderly participation in adjuvant anti-HER2 trials

Trial	Regimen	Median age	Elderly patients
HERA (19)	Trastuzumab 1–2 y vs. observation	49 vs. 49 y	≥60 y =16.2% vs. 16.2%
BCIRG–0006 (16)	ACT vs. ACTH vs. TCH	Not reported	Not reported
NCCTG N9831 (20)	ACT vs. ACTH	Not reported	≥60 y =16.1% vs. 18.9%
NSABP B31(20)	ACT vs. ACTH	Not reported	≥60 y =16.2% vs. 16.4%
APT (21)	Paclitaxel + trastuzumab	Not reported	60–69 y =23.6%; ≥70 y =10.1%
ALTTO (12)	Trastuzumab vs. trastuzumab + lapatinib vs. lapatinib vs. trastuzumab – lapatinib	All arms 51 y	≥65 y =10% all arms
APHINITY (11)	Trastuzumab vs. trastuzumab + pertuzumab	Not reported	≥65 y =12.2% vs. 13.1%
ExteNET (22)	Neratinib vs. placebo	52 vs. 52 y	≥60 y =25% vs. 25%

A, anthracycline; C, cyclophosphamide; T, taxane; H, trastuzumab; y, year; vs, versus.

many elderly patients (28), and, nowadays, for lower risk tumours (<3 cm and node-negative disease), the weekly paclitaxel/trastuzumab regimen is a probably a safer and very effective option (21). As anti-HER2 therapy advances and dual blockade (and new agents such as neratinib) are incorporated into clinical practice in the adjuvant setting, elderly-specific or, at the very least, trials including a considerable number of elderly patients into the sample and elderly specific end-points will be direly needed.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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