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Original article

Trastuzumab for patients with HER2 positive breast cancer: Delivery, duration and combination therapies

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A B S T R A C T

With the exception of endocrine therapy, no other systemic treatment of patients with breast cancer has reached such a magnitude of beneficial effect as trastuzumab. This targeted agent (monoclonal antibody) is associated with a significant improvement in both disease-free (DFS) and overall survival (OS) in women with HER-2 positive breast cancer when given in combination with or in sequence to adjuvant chemotherapy. This has been confirmed in a recent Cochrane meta-analysis of randomized controlled trials (RCTs), including 6 adjuvant and 2 neoadjuvant studies (NSABP B-31, NCCTG N9831, BCIRG 006, HERA, FinHer, PACS-04, Buzdar and NOAH), with data collection until February 2010. Overall, mortality is reduced by one-third and the risk of relapse by 40%.

Concerns regarding cardiac dysfunction are declining, with reports indicating its reversibility in most instances, however truly long term cardiac evaluation is still lacking.

Hence, the benefit of trastuzumab could be challenged by cardiac toxicity, in lower-risk patients [T1a,b node-negative (N0) tumors] or those with increased cardiovascular risk (older women and patients with previous significant heart disease/suboptimal left ventricular ejection fraction [LVEF (<55%)], all of whom were largely excluded from the aforementioned adjuvant RCTs. These patient subgroups might warrant a specific approach, such as anti-HER2 treatment combined with just a taxane (avoiding anthracyclines) or with endocrine therapy. Reasonably large phase II trials aimed at exploring these more individualized regimens are underway in the US.

The optimal duration of trastuzumab therapy remains unknown since the selection of the one year duration in the pivotal trials was arbitrary. The HERA trial showed that prolonging trastuzumab administration to two years does not confer additional advantage over one year. The PHARE trial compared 6 versus 12 months of trastuzumab and failed to show non-inferiority of the shorter treatment administration. At the present time, one year of adjuvant trastuzumab remains the standard-of-care until results from SOLD, Short-HER and PERSEPHONE consolidate or negate this finding.

The route of trastuzumab administration has also been recently challenged. A subcutaneous formulation is being evaluated in several studies. The HannaH phase III trial compared the subcutaneous (SC) to the intravenous (IV) formulation of trastuzumab. The former was proven non-inferior to the latter, although the incidence of serious adverse events was slightly higher in the SC arm. The authors concluded that SC trastuzumab, administered at a fixed dose of 600 mg over 5 min, is a valid alternative option, with the potential for human and economic savings in clinical practice.

1. Introduction

Trastuzumab, a humanized monoclonal antibody against the extracellular domain of the HER2 receptor, is the standard-of-care treatment for patients with early HER-2 positive breast cancer when given concomitantly or in sequence to adjuvant chemotherapy. Although this treatment has been in routine use for nearly 7 years now, some issues are still controversial, specifically, the timing of the addition of trastuzumab to the chemotherapy regimen (simultaneously or sequentially), the preferred chemotherapy backbone in this setting, the administration of adjuvant trastuzumab for tumors smaller than 1 cm and, more recently, the

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ideal route for trastuzumab administration (intravenous or subcutaneously). In addition to these issues, this article will also summarize the recently updated data of some of the major pivotal trials.

2. Optimal trastuzumab duration

Trastuzumab has improved both disease-free (DFS) and overall survival (OS) in patients with early HER-2 positive breast cancer with moderate-to-high risk of recurrence, when given in combination with or in sequence to adjuvant chemotherapy [1,2]. Individual trials showed a benefit in terms of DFS and most of them in terms of OS. A recent meta-analysis published by the Cochrane group [3] included 6 adjuvant and 2 neoadjuvant randomized controlled trials (RCTs), namely NSABP B-31, NCCTG N9831, BCIRG 006, HERA, FinHer, PACS-04, Buzdar and NOAH. This meta-analysis [3] involves 11,991 patients with a variable follow-up of 18–65 months (data collection was performed until February 2010). The combined hazard ratio (HR) for overall survival (OS) was 0.66 [95% confidence internal (CI95%) 0.57–0.77, $P < 0.00001$] while the combined HR for disease-free survival (DFS) was 0.60 [CI95% 0.50–0.71, $P < 0.00001$], illustrating the major benefit conveyed by trastuzumab in this patient population.

In 2012, updated results from the HERA [4,5] and from the American Joint Analysis (NSABP B-31 and NCCTG N9831) [6] trials were very reassuring, both in terms of efficacy and in terms of cardiac safety of the adjuvant standard regimen of one year of trastuzumab.

The HERA trial was the only trial exploring longer trastuzumab administration duration: 2 years versus 1 year. In the latest analysis [4,5], HERA showed no benefit for the prolongation to 2-year trastuzumab given as sequential treatment following standard (neo)-adjuvant chemotherapy (see Table 1). Furthermore, patients on this longer administration arm also experienced a higher rate of asymptomatic or mildly symptomatic cardiac events (7.2% versus 4.1%, respectively), without an increase in severe cardiac toxicity. Interestingly, a plateau in the number of cardiac events was reached after 2 years, implying that patients experiencing cardiac dysfunction are mostly likely to experience it during trastuzumab administration rather than in the follow-up period. The updated intent-to-treat analysis of the comparison of 1 year trastuzumab versus observation at 8 years of median follow-up (see Table 1) demonstrates a statistically significant improvement in DFS and OS for the standard one year of trastuzumab, despite a high crossover rate of 52.1% and erase the concern of an attenuation of benefit seen in previous reports with a shorter follow-up.

Contrasting with HERA, the PHARE trial conducted in France tested a shorter duration of adjuvant trastuzumab [7, 8]. PHARE is a non-inferiority trial involving 3380 women treated with adjuvant chemotherapy regimen of at least 4 cycles and then being randomized to continue trastuzumab for a total of 12 months or to halt it after the completion of 6 months of therapy. This study did not reach its primary endpoint since the margins of the HR confidence interval crossed the 1.15 boundary for significance (refer to Table 1). In other words, non-inferiority of the 6 months was not demonstrated, and although there was a suggestion for greater efficacy at one year of treatment, the initial follow-up in that trial is still suboptimal The results of other phase III RCTs looking at shorter trastuzumab duration are still pending: SOLD (9 weeks versus 1 year of trastuzumab; NCT00593697), Short-Her (3 months versus 1 year of trastuzumab; NCT00629278), Persephone (6 months versus 1 year of the antibody; NCT00712140), and the Hellenic Group trial (also 6 months versus 1-year of trastuzumab; NCT00615602). It is likely that a meta-analysis of all these trials will have enough power to reach a robust conclusion.

3. Concomitant or sequential administration

The benefit of adding trastuzumab to the adjuvant chemotherapy protocol has been proven whether the antibody is given concomitantly with taxanes (Joint Analysis [9,10] and BCIRG 006 [11] studies), after chemotherapy completion (arm B of N9831 [12] and HERA) or even with an anthracycline-free regimen [11] (BCIRG 006). Although the only direct comparison available (arms B and C of the NCCTG N9831 trial) showed a trend favoring the concomitant administration, it did not reach formal statistical significance [12]. Comparisons across studies, should be taken with caution but seem to point out in the direction of a higher efficacy of the concomitant administration. The PHARE trial also examined this issue and prespecified subgroups analyzes results follow the same direction: the shorter sequential administration had a detrimental effect for

Table 1
Updated DFS and OS of the major adjuvant trials in HER2-positive early breast cancer.

Abbreviated study name	Patients (*n*)	Simplified treatment schema[a]	H duration (weeks)	Timing of H administration	Median follow-up (months)	Disease-free survival		Overall survival	
						HR[b]	*p* value	HR[b]	*p* value
HERA	1698	CT	–	–	96	0.76	<0.0001	0.76	0.0005
	1703	CT → H	52	Sequential					
	1701	CT → H	104	Sequential		0.99	0.86	1.05	0.63
Joint analysis NSABP-B31 NCCTG N9831					100.8	0.60*	<0.0001	0.63*	<0.0001
	2018	AC → P	-	–					
	2028	AC → PH → H	52	Concurrent					
NCCTG N9831	1087	AC → P	–		72	0.67[c]	<0.001	0.88	0.343
	1097[c]/954[d]	AC → P → H	52	Sequential					
	949	AC → PH → H	52	Concurrent		0.77[d]	0.022	0.78	0.102
BCIRG 006	1073	AC → D	–	–	65	0.64[e]	<0.001	0.63	<0.001
	1074	AC → DH → H	52	Concurrent					
	1075	DCarboH → H	52	Concurrent		0.75[f]	0.04	0.77	0.038
PHARE	1690	CT + H	26	Concurrent/	42.5	1.28	0.29	1.47	NR
	1690	CT + H	52	Sequential					

[a] Referring to the chemotherapy backbone and trastuzumab only. Details of radiotherapy and hormonal therapy are not given here.
[b] Unadjusted hazard ratios (except for the HRs of the Joint Analysis* which are adjusted).
[c] HR and number of patients of AC → P versus AC → P → H.
[d] HR and number of patients of AC → P → H versus AC → PH → H.
[e] Comparison between AC → D versus AC → DH → H.
[f] Comparison between AC → D versus DCarboH → H.