PublisherInfo		
PublisherName	:	BioMed Central
PublisherLocation	:	London
PublisherImprintName	:	BioMed Central

Phase III trial of chemotherapy ? HerceptinR in metastatic breast cancer

ArticleInfo		
ArticleID	:	3766
ArticleDOI	:	10.1186/bcr-2001-68448
ArticleCitationID	:	68448
ArticleSequenceNumber	:	38
ArticleCategory	:	Paper Report
ArticleFirstPage	:	1
ArticleLastPage	:	3
ArticleHistory	:	RegistrationDate : 2001–8–20 Received : 2001–4–27 Accepted : 2001–8–20 OnlineDate : 2001–9–12
ArticleCopyright	:	Biomed Central Ltd2001

ArticleGrants	:	
ArticleContext	:	1305833

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Keywords

Breast cancer, Herceptin, HER2, phase III trial

Context

Despite advances in diagnosis and treatment, breast cancer still remains a major cause of cancer deaths. Metastatic breast cancer (MBC) is virtually incurable, with median survival of 18 to 24 months. The HER2 gene encodes a growth factor membrane receptor that is overexpressed in 25-30% of MBC cases and is associated with aggressive metastasis and poor prognosis. Transtuzumab (HerceptinR) is a humanised monoclonal antibody against HER2 that has proven efficacy as a single-agent therapeutic for MBC. This randomised phase III trial analysed the effect of adding transtuzumab to standard first-line chemotherapy (CT) for MBC.

Significant findings

In an intention-to-treat analysis, the addition of transtuzumab was associated with statistically significant and better results for time to disease progression (7.4 months versus 4.6 months; $P < 0.001$), response rate (50% versus 32%; $P < 0.001$), duration of response (9.1 months versus 6.1 months; $P < 0.001$) and overall survival (25.1 months versus 20.3 months; $P = 0.046$). Similar differences were seen in both chemotherapy subgroups (anthracycline-based and paclitaxel), although for overall survival the *P*values were 0.16 and 0.17, respectively. Addition of transtuzumab was also associated with higher cardiotoxicity than that for CT alone, particularly in the anthracycline-based subgroup and in patients who had received adjuvant anthracyclines. After a median follow-up of 30 months the authors concluded that transtuzumab increases the clinical benefit of first-line CT in MBC and reduces the relative risk of death by 20%.

Comments

The magnitude of transtuzumab's effect on patient survival in this study may have been reduced by the crossover of patients from randomised to open-label treatment. This change in regimen occurred for 66% of patients, whose cancer had progressed and thus required treatment with transtuzumab. Furthermore, patients eligible for this study included those with tumours with different levels (2+ and 3+ of HER2 overexpression. A better selection of patients, namely only HER2 3+ by IHC or HER2 2+ by FISH could have allowed a more accurate assessment of transtuzumab benefit. Cardiac dysfunction is an important and troubling side effect of transtuzumab treatment, particularly in patients who have had, or who receive, concomitant anthracycline-based CT; in these patients the cardiotoxicity of anthracycline-based agents is already a concern. This study confirms transtuzumab as one of the few anticancer agents associated with an important survival benefit in MBC. Establishing its role in the adjuvant setting is essential. Clinical trials are already ongoing in the US, and will soon begin in Europe.

Methods

Immunohistochemical IHC analysis of HER2 positivity, randomised phase III clinical trial, intention-to-treat analysis, Kaplan-Meier and two-sided log-rank tests

Additional information

References

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