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Meta-analysis of taxanes alone or in combination with anthracyclines versus non taxane-based regimens as first-line therapy of patients with metastatic breast cancer (MBC): a lesson from the past and a message for the future

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Introduction: After a decade of randomized clinical trials, clear guidelines for the optimal use of taxanes in MBC are still lacking, in part because of inconsistency in the results generated and the lack of an overall survival benefit in most trials.

We thought that a meta-analysis of *individual* patient data from all relevant trials investigating advantages of taxanes (sequenced or combined with anthracyclines) in *first-line* treatment of patients with MBC might disclose a survival benefit overall or in the subset of patients with visceral metastases. We also investigated whether tumor response and PFS were surrogate endpoints of OS in this setting.

Material and Methods: We succeeded in collecting key individual patient data for all 3953 patients randomized in 11 trials. Odds ratio of non response and hazard ratios for progression-free survival (PFS) and overall survival (OS) were estimated in each trial.

Results: In the entire patient population (n = 3953), the median follow-up is 41 months, the median PFS 7 months and the median OS 19 months. Information on sites of disease (eg visceral vs non visceral) could be obtained in 2519 women. A total of 3034 women contributed to the comparison of taxane-anthracycline combinations versus anthracycline regimens, while 919 were enrolled in trials comparing single agent taxanes to single agent anthracyclines.

The table summarizes the results in terms of "non-response" odds ratios, PFS hazard ratios and OS hazard ratios in the entire group (taxane versus no taxane).

	Non-response	PFS	OS
Odds/Hazard ratio[a]	0.73	0.98	0.97
p-value for test of treatment effect	0.006	0.52	0.34
p-value for test of heterogeneity	<0.001	<0.001	0.09
p-value for test of interaction (combination vs. single-agent regimen)	<0.001	0.001	0.49

[a]Odds ratio for Non-response, hazard ratio for PFS and OS.

The analysis of treatment effects in the subgroups with or without visceral disease did not reveal a "subgroup" benefit for either PFS or survival. Tumor response was found to be predictive of longer PFS and longer OS while PFS was poorly correlated with OS. Treatment effects on response did correlate with treatment effects on PFS but not on OS. Finally, treatment effects on PFS were poorly correlated with treatment effects on OS.

Conclusion: This metaanalysis of empirical trials conducted in the past century failed to disclose a survival gain associated with the introduction of taxanes in first line chemotherapy regimens for MBC but firmly establishes their contribution to higher chances of response.

Clinical judgment remains the best guide for chemotherapy selection in the advanced disease setting. Tailored trials asking relevant biological questions are the way forward. The results of the current analysis indicate that tumor response could be an acceptable surrogate for PFS but no endpoint would be a good surrogate for OS in these trials.

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Adjuvant chemotherapy treatment tailoring

Abstract not received.

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Herceptin adjuvant trials – 2006 update

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HER2 overexpressing breast cancers display an aggressive clinical course. Trastuzumab (Herceptin)a recombinant monoclonal antibody against HER2, improves the survival in women with advanced HER2 overexpressing breast cancer. In order to test the hypothesis of whether its use in the adjuvant setting may prolong survival, four large multicenter trials were designed to test the role of trastuzumab as adjuvant therapy after surgical treatment of primary breast cancer. These trials have enrolled over 11,000 patients and their initial results have been recently reported (the HERA trial, the combined analysis of the B-31 and N9831 studies, and the BCIRG006 study) [1–3]. Importantly, these trials had different designs that looked at the trastuzumab question from different angles: The HERA trial was a pure sequential study with trastuzumab given for 1 or 2 years after the chemotherapy of choice; the B-31 and N9831 trials were anthracycline and taxane-based and included one arm with concomitant administration of a taxane and trastuzumab. Finally, the BCIRG study had a non-anthracycline containing arm. With a very brief follow-up (one to two and a half years), all four trials show highly significant reductions in the risk of recurrence. The HERA trial at a one year of follow up shows a 46 percent reduction in risk and an absolute benefit in terms of disease-free survival at 2 years of 8.4%. The trials B-31 and N9831 result in a risk reduction of a breast cancer event at 3 years by 52% and with a longer follow than the HERA trial shows a survival advantage. Finally, the BCIRG at a median follow up of 23 months shows an improvement in disease free survival of 51% in the trastuzumab-anthracycline containing arm and of 39% in the trastuzumab non-anthracycline arm (no statistically significant difference between the 2 trastuzumab containing arms)Unresolved questions remain. What is the optimal schedule for therapy with trastuzumab: should it be given simultaneously with or sequentially after chemotherapy? What is the nature and reversibility of cardiac dysfunction? The data so far provides reassuring information about recovery and symptomatic control of heart failure in the majority of patients, although longer follow up is required. It will also be important to have a longer follow up in the non-anthracycline containing arm in the BCIRG trial. Finally, the adequate duration of trastuzumab administration is still unknown.

In the meantime, the results of the these 4 are sufficiently compelling to consider adjuvant trastuzumab as a standard option at completion of locoregional therapy and (neo) adjuvant chemotherapy for women who fulfil the study eligibility criteria for these trials.

References

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Friday, 24 March 2006 11:00–12:45

KEYNOTE SESSION

Metastatic breast cancer – are guidelines possible?

438 Invited

Consensus on medical treatment of metastatic breast cancer: a Central European initiative

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Breast cancer is the most common malignancy among women in the Western hemisphere. Whereas a series of consensus statements have established neoadjuvant and adjuvant treatment as state-of-the-art management in early breast cancer, there have been virtually no internationally accepted recommendations on therapy of MBC. Treatment of MBC aims primarily at improving the quality of life by prevention and palliation of symptoms, and at prolongation of survival. Medical treatment of MBC may include endocrine agents, cytotoxic chemotherapy, "targeted therapies", bisphosphonates, and supportive measures. Treatment choices for MBC are guided by several factors, in particular by hormone receptor