Proffered Papers

Breast cancer II

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A phase III randomized trial of bendamustinehydrochloride, methotrexate, and 5-FU (BMF) versus CMF as first-line treatment of patients with metastatic breast cancer

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Background: Bendamustine is a bifunctional agent with alkylator and purine-like properties agent that has shown superior antiproliferative *in vitro* effectivity and preliminary improved clinical effect compared to Cyclophosphamide. The replacement of Cyclophosphamide by Bendamustin in the CMF-regimen was prospectively tested in this randomized, phase III pivotal trial.

Patients and Methods: 364 patients with metastatic breast cancer, not previously treated for metastatic disease by chemotherapy have been randomized to either BMF (Bendamustine 120 mg/m*, Methotrexate 40 mg/m*, 5-FU 600 mg/m*) or CMF (Cyclophosphamide 500 mg/m* instead of Bendamustine). The same treatment was given on day 1 and 8, and was repeated on day 29. Primary aim of the study was to improve the time to progression.

Results: A significant difference in median time to progression was observed in favour for the BMF group (8.2 months) compared to CMF group (6.7 months). Moreover, effect of BMF on TTP became highly significant in the stratum "prior adjuvant therapy in patients with non-visceral metastases" (p=0.034). Confirmed clinical responses were observed with equal frequency (19.8% vs 18.0%) in both treatment arms. A non statistically significant difference in t he duration of response of 14.8 (BMF) and 10.3 (CMF) months was recorded (p=0.076). Leucopenia (62.7% vs. 40.0%), thrombopenia (32.0% vs 10.3%) and stomatitis (44.4% vs 24.3%) were more frequent in the BMF arm, whereas alopecia (11.2% vs 17.8), amenorrhea (10.1 vs 17.3%), and constipation (10.7% vs 18.4%), were more frequent in the CMF group. The incidence of CTC grade 4 toxicities was higher in the BMF arm compared to the CMF group, whereas the incidence of grade 3 toxicities was equally distributed (36% vs. 31%). No differences in quality of life between the two treatments was detected.

Conclusions: The substitution of Cyclosphosphamide by Bendamustine in the "CMF" regimen can significantly increase anti-tumor activity in patients with metastatic breast cancer. The modified treatment regimen showed an acceptable toxicity and should be further explored in early stages of this disease.

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Phase III comparison of docetaxel (D)and paclitaxel (P) in patients with metastatic breast cancer (MBC).

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Docetaxel and paclitaxel are among the most active agents for the treatment of patients (pts) with MBC. In randomized studies, the reported response rates for D have ranged from 30-48% and for P (3-hour infusion) from 16-29%. We report the first direct comparison of D to P in pts with MBC after failure of anthracyclines.

Methods: Between 1994 and 2001, 449 women were randomized to either D 100 mg/m2 (1-hour infusion) q 3 wks or P 175 mg/m2 (3-hour infusion) q 3 wks. Eligibility criteria included: bi-dimensionally measurable MBC; and, either 1 prior anthracycline-based regimen as first-line therapy for MBC or disease progression during or within 12 months of completing anthracycline-based adjuvant or neoadjuvant chemotherapy.

Results: The arms were well balanced for (D vs P): median (med) age (56 vs 54); med KPS (90% vs 90%); hormone receptor positivity (56% vs 50%). Intent-to-treat (ITT) analysis was performed for the major efficacy endpoints.

ITT	D (n=225)	P (n=224)	p-value
ORR	32.0%	25.0%	0.10
CR	2.2%	5.4%	
PR	29.8%	19.6%	
SD	38.2%	39.7%	
PD	16.9%	29.0%	
Med TTP	5.7mos	3.6mos	<0.0001
Med OS	15.4mos	12.7mos	0.03

In the analysis of 388 eligible pts evaluable for response, the ORR was D=37.4% vs P=26.4% (p=0.02), and D maintained its statistical superiority in TTP and OS. 444 pts received drug and were evaluable for safety, 222 pts on each arm. Mean and med # of cycles administered was 6.1 and 6 (D) vs 5.8 and 4 (P). Grade 3/4 toxicities for D vs P: neutropenia 93.3% vs 54.5%; asthenia 23.9% vs 6.8%; infection 14.0% vs 5.0%; edema 11.3% vs 4.5%; stomatitis 10.4% vs 0.5%; neuromotor 9.0% vs 4.5%; neurosensory 8.6% vs 4.5%.

Conclusion: The ORR was higher for D than for P, and this difference approached statistical significance in the ITT analysis. TTP and OS were statistically superior for D. Treatment with D was associated with an increased incidence of grade 3/4 toxicities.

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Phase III study comparing AT (Adriamycin, Docetaxel) to FAC (Fluorouracil, Adriamycin, Cyclophosphamide) as first-line chemotherapy (CT) in patients with metastatic breast cancer (MBC)

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Introduction: In a multicenter phase III study we compared the efficacy and safety of six cycles of AT (50/75 mg/m^2) to FAC (500/50/500 mg/m^2) each given on day 1, q3 weeks as first-line chemotherapy in MBC.

Material and methods: The study was performed in 1 academic and 18 community hospitals in the southwest Netherlands. Adjuvant anthracycline treatment up to a cumulative dose equivalent to 240 mg adriamycin/m^2 was allowed. Patients on AT received ciprofloxacin prophylaxis.

Results: Between 03/97 en 04/02, 216 patients were randomized. Patient and tumor characteristics were balanced; median (med) age 53 years, med. performance status WHO 0, adjuvant CT 33%, ≥ 3 tumor sites involved 72%; visceral (lung/liver) disease 67%. Med. follow-up was 22 months.

The only significant difference in severe (III/IV, WHO) toxicity, in the current analysis, is the incidence of febrile neutropenia, AT 34%, FAC 9,7% of the patients (p < 0.001) and 7.5% and 2% of all cycles, respectively (p<

	AT (n=104)		FAC (n=103)
Overall response (OR)	62%	38%	p=0.001
CR	4%	1%	
PR	58%	37%	
CR+PR+SD ≥ 6 months (clinical benefit)	77%	62%	p=0.02
Med. duration of OR (months)	8.3	8.2	
Med. progression-free survival (months)	7.7	7.0	