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Systemic High-dose Intravenous Methotrexate for Central Nervous System Metastases in Breast Cancer

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Background: Currently, there is no standard chemotherapy for patients (pts) with breast cancer (BC) brain metastases (BM). Infusion of high-dose intravenous methotrexate (HD MTX) has been demonstrating to penetrate the blood-brain barrier. The aim of this trial was to assess the efficacy and safety of HD MTX in pts with BC BM.
Patients and Methods: Patients with BC BM were treated by HD MTX (3 g/m^2) during 3 hours infusion and concomitant hyper alcalin hydration. A rescue by intravenous folinic acid was started 24 hours after the completion of MTX until the blood concentration of MTX decreased below 0.05 μmol/l M. A pharmacokinetic assessment was performed to achieve a PK-PD study. Radiographic and clinical response rate, time to progression (TTP), overall survival (OS), and safety were assessed.
Results: Between April 2004 and October 2009, 22 patients with a médian age of 59 years (range 37−84) were treated with 67 cycles of HD MTX (median 3, range 1−7). BM were parenchymal metastases and leptomeningeal metastases in 17 and 8 cases, respectively.
All pts were assessable for response (22 and 18 pts for CNS and other metastatic sites, respectively). Two pts (9%, 95% CI 2.5–27.8) achieved a partial response, 10 (45%, 95% CI 27−65) showed disease stabilization, and 10 (45%, 95% CI 27−65) had disease progression in CNS. The response in others metastatic site was: 7 pts (39%, 95% CI 20.3–61.4) achieved a disease stabilization, and 11 pts (61%, 95% CI 38.6–79.6) had disease progression. At a median follow up of 11 months, TTP and OS were 2.1 (95% CI 1.4−2.9) and 6.3 (95% CI 1.8−10) months, respectively.
HD MTX was well tolerated without grade 4 non haematological toxicities. Common grade 3 non haematological toxicities were: 4 (18%) elevated sérum hepatic transaminases and 2 (9%) stomatitis. Grade 3−4 haematological toxicity was observed in 4 pts (18%): 3 (13.5%) thrombocytopenia, 3 (13.5%) neutropenia et one patient (4.5%) with anemia.
Conclusion: HD MTX demonstrated a moderate activity at 3 g/m^2. Nonetheless, the favorable toxicity profile has been suggesting the possibility to increase the dosage and further study are planned.

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Albumin-bound Paclitaxel (ab-pac) Versus Docetaxel for First-line Treatment of Metastatic Breast Cancer (MBC): Overall Survival (OS) Subset Analyses of a Randomized Phase 2 Trial

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Background: We previously reported the results of a Phase II study evaluating the efficacy and safety of 3 different dosing regimens of ab-pac and docetaxel for the first-line treatment of MBC (Gradishar et al. *J Clin Oncol*. 2009;27:3611). Final overall survival outcomes will be reported (ASCO-Breast 2011). Here we report final OS values in specific patient subgroups.
Materials and Methods: Patients (N = 300) with previously untreated MBC were randomized to 1 of 4 treatment arms (listed in table). A step-down statistical approach was used for pairwise comparisons of treatment groups.
Results: Median OS values are shown in the table. For all patients, Arm C produced a longer median OS than arm B (HR 0.575; $P = 0.008$) or arm D (HR 0.686; P not statistically significant). Although the study was not powered to detect a significant difference in OS within subgroups, the trend in OS benefit of arm C vs. arm B was consistent among various patient subgroups. Safety results showed that grade 4 neutropenia was significantly less frequent in the ab-pac arms vs. the docetaxel arm (5−9% vs. 75%; $P < .001$). Rates of grade 3 sensory neuropathy (SN) were 21%, 9%, 22% and 12%, respectively in arms A, B, C, and D (P = 0.082). No grade 4 SN occurred in ay of the arms. Subgroup analyses revealed that safety profiles were similar to those in the overall patient population.

	OS (months)								Overall P-value[a]
	ab-pac						Docetaxel		
	A 300 mg/m^2 q3w		B 100 mg/m^2 qw 3/4		C 150 mg/m^2 qw 3/4		D 100 mg/m^2 q3w		
	n	Median	n	Median	n	Median	n	Median	
All patients	76	27.7	76	22.2	74	33.8	74	26.6	0.047
<65 years	67	27.7	62	23.0	64	32.8	55	21.4	0.171
⩾65 years	9	>30.5	14	17.3	10	>45.9	19	31.3	0.170
DM									
Visceral	64	27.1	61	19.6	59	32.1	67	21.4	0.093
Nonvisceral	12	36.0	15	29.7	15	>48.4	7	>35.4	0.405
Lesion sites									
<5	39	29.5	37	23.0	38	34.3	41	30.2	0.240
⩾5	25	21.7	24	14.7	21	29.1	26	18.0	0.290
Premenopausal	26	26.7	14	15.6	21	32.1	12	>35.4	0.399
Postmenopausal	49	36.0	62	23.7	53	38.7	60	28.2	0.134

DM, dominant metastasis; OS, overall survival; q3w, every 3 weeks; qw 3/4, first 3 out of 4 weeks.
[a]By log-rank test.

Conclusion: Among patient subgroups, a trend in OS benefit for ab-pac 150 mg/m^2 qw 3/4 was consistent with the benefit observed in the overall patient population. This trend was observed regardless of age, visceral disease status, number of lesions, or menopausal status. The ab-pac 150 mg/m^2 qw 3/4 dosing regimen may provide the best clinical outcomes for MBC, even for difficult-to-treat patients.

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Impact of Systemic Anti-Her2 Treatment on Overall Survival in Patients With Brain Metastases From Her2-overexpressing Breast Cancer

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Background: Brain metastases (BM) are frequently diagnosed in patients with Her2-overexpressing breast cancer. We have previously reported that trastuzumab-based treatment after diagnosis of BM may improve overall survival due to prolonged systemic disease control. Based upon those results, we investigated whether lapatinib, a small molecule tyrosine-kinase inhibitor, may yield additional survival benefit.
Methods: Eighty consecutive patients treated for BM from Her2-positive breast cancer were identified from a breast cancer database. Karnofsky Performance Score (KPS) ⩾70 was required, as low KPS is a known negative predictor of survival. Thirty-seven patients were treated before 2003, when routine application of trastuzumab after diagnosis of BM was started and served as control. Reminders received either trastuzumab or lapatinib and trastuzumab (either concomitantly or sequentially) with or without chemotherapy after local therapy for BM.
Her2 was determined by immunohistochemistry and reanalyzed by FISH if a score of 2+ was gained. Overall survival (OS) from diagnosis of BM was defined as primary study endpoint and calculated using the Kaplan–Meier method. A Cox proportional hazards model was applied to correct for confounders significantly associated with OS in the univariate model.
Results: Median OS in patients with BM from Her2-positive breast cancer receiving trastuzumab after radiotherapy was 13 months (95% CI 8.85–17.15). Corresponding numbers were 9 months in patients treated with chemotherapy, and 3 months with radiotherapy alone. After a median follow-up of 24 monts, median OS was not reached in patients receiving lapatinib. Addition of lapatinib significantly prolonged OS over trastuzumab alone ($p = 0.002$). After correction for visceral metastases, >2 metastatic sites, KPS, and number of brain metastases, additional treatment with lapatinib remained a significant predictor for better outcome (HR 0.279; 95% CI 0.1–0.76; $p = 0.012$).
Conclusions: In this retrospective single-centre non-randomized study, the addition of lapatinib improved survival in patients with brain metastases from Her2-positive breast cancer. We therefore suggest that patients with KPS ⩾70 should receive lapatinib in addition to trastuzumab after completion of local therapy, as it yielded an ameliorated outcome as compared to trastuzumab-based therapy alone.