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Active specific immunotherapy with NGcGM3/ VSSP/ Montanide ISA-51 (CIMAVaxG) vaccine in the treatment of patients with metastatic breast cancer: Results of a randomized phase II clinical trial

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The search for new therapeutic weapons that cause an increase in the survival of the patients suffering from MBC, preserving their quality of life, prevails. The results obtained with the CIMAVaxG vaccine in Phase I clinical trials in patients with metastatic melanoma and advanced breast cancer evidenced that the vaccine was safe and immunologically effective.
A randomized phase II clinical trial study of 80 Patients with MBC diagnosis was performed. Arm I: Treated with CIMAVaxG vaccine and Arm II: Treated with best supportive care after achieving clinical control disease (CR+PR+SD according the Recist criteria) with the standard first line onco-specific therapy established in the Oncology Therapeutic Guidelines (NCCN v.1.2007).
The primary endpoint of the clinical trial was the survival rate at 18 months (SR) and the secondary endpoints were time to progression (TTP) and overall survival (OS). The vaccination schedule was 15 vaccine doses of 200 mg by intramuscular route, completing one year of treatment.
As for all up to now tested therapeutic cancer vaccines, CIMAVaxG mostly benefited one subgroup of patients: those with non-visceral metastasis. In this subgroup of patients (70% of all the MBC patients) vaccination significantly increased the survival rate at 18 months in 18.9% ($p = 0.049$, Breslow test). Interestingly, even with a suboptimal schedule of administration during 1 year CIMAVaxG was capable to notably increase OS survival in this subgroup of patients (a median survival in vaccine group of 26.17 months while for control group was 12.17 months). Nevertheless, this outstanding difference in OS did not reach statistical significance due to the small number of patients (50 patients).
CIMAVaxG vaccine was able to induce specific NGcGM3 (IgM and IgG) antibodies in vaccinated patients. CD4 down modulation in T cells from normal PBMC, caused by the incorporation of NGcGM3, was only reverted when the cells were incubated with the sphyngolipid in the presence of sera obtained from vaccinated patients in which anti-NGcGM3 specific antibodies were detected.
Summarizing, these results include CIMAVaxG in the closely selected group of treatments capable of increasing survival in metastatic breast cancer patients.

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HER2 significance and treatment outcomes after radiotherapy for brain metastases in breast cancer patients

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Background: To investigate the management and outcome of breast cancer patients developing brain metastases according to HER2 status.
Materials and Methods: A retrospective review of 265 patients records receiving whole brain radiotherapy (WBRT) for metastatic breast cancer between June 2002 and December 2006 at the Royal Marsden Hospital was performed. Patients were stratified into two cohorts according to HER2 status. Clinical and biological characteristics at time of diagnosis were analysed. Time to diagnosis of brain metastases, presence of systemic disease, treatment and overall survival (OS) after WBRT were studied.
Results: 181 patients had HER 2 status recorded: 88 were HER2 positive (HER2+) (49%) and 93 (51%) HER2 negative (HER2−). The median age at initial diagnosis was 50 years and 47 years in the HER2+ and HER2− groups respectively. Initial stage, grade and pathology were similar in the 2 groups. No difference in ER/PR status was seen between the 2 groups. Median time to diagnosis of brain metastases was 36.7 months (mo) (range 0–230) for HER2+ and 48.5 mo (range 0–211) for HER2− patients. HER2+ patients were more likely to have liver 48 (54%) vs 36 (38%) $p = 0.04$ and bone 42 (47%) vs 30 (32%) $p = 0.05$ metastases at diagnosis of brain metastases than HER2-. 72 (82%) HER2+ group developed brain metastases whilst on chemotherapy compared with 45 (48%) in HER2− group. Management of cerebral metastases in the two groups differed. (See Table) Median survival WBRT was 8 mo (1−38) for HER2+ patients and 4 mo (1−64) for HER2− patients ($p = 0.01$). On univariate analysis only performance status (PS) $p = 0.01$ was a significant predictor of longer OS, while those with lung metastases had shorter OS $p = 0.02$. Presence of liver disease was unrelated to survival. On multivariate analysis after adjusting for PS, bone and lung metastases, HER status remains an independent prognostic factor ($p = 0.02$). On brain metastasis progression, 18 (20%) of HER2+patients received stereotactic radiotherapy, gamma knife radiosurgery or further WBRT, compared with 6 (6%) in HER2− group.

	HER2+ (n = 88)	HER2− (n = 93)	p value
RT Dose <20 Gy/20 Gy/>20 Gy	1/88/3	2/84/6	0.6
Surgery	5 (6%)	2 (2%)	0.3
Chemotherapy	55 (64%)	39 (42%)	0.004
Further RT/Stereotactic RT	18 (20%)	6 (6%)	0.008

Conclusion: HER2+ patients had a better survival; this could be attributed due to a more aggressive approach in their management with combined cytotoxic chemotherapy and ongoing Trastuzumab.

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Pooled analysis of skin and diarrhea events in cancer patients treated with lapatinib

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Background: Lapatinib (Tykerb®/Tyverb™, GlaxoSmithKline) is a small molecule tyrosine kinase inhibitor of epidermal growth factor receptor EGFR (ErbB1) and HER2 (ErbB2) that was recently approved for the treatment of women with HER2+ metastatic breast cancer who received prior therapy including an anthracycline, a taxane, and trastuzumab. To date, lapatinib has been administered to >5,000 patients in clinical trials. This presentation describes the characteristics of skin events (SE) and diarrhea events (DE) in lapatinib-treated patients.
Materials and Methods: Eight lapatinib clinical trials in patients with metastatic breast cancer or other tumor types were reviewed. Lapatinib doses ranged from 1,000 to 1,500 mg/day as monotherapy (n = 928) or in combination with tamoxifen (n = 197) or capecitabine (n = 191). Skin events were predefined as dermatitis, drug eruption, dry skin, pruritus/urticaria, skin disorder, skin infection, nail, and hair disorder. All events were characterized based on CTC grading, and examined regarding their relationship to dose, time to onset, duration, required interventions, and outcomes.
Results: Among 1,126 patients, 54% experienced SE and 50% experienced DE. The majority of SE and DE were CTC grade (G) 1 or 2 (SE: G1 55%, G2 35%; DE: G1 54%, G2 30%). There were no grade 4 SE and <1% of patients reported grade 4 DE. Early onset was most common: SE, 45% during days 1−14; DE, 44% in <6 days from start of treatment. The median duration was 29 days for SE and 5 days for DE. The most common SE was dermatitis (G1−3, 38%). Among all patients, only 3% reported G3 dermatitis. Dose interruption or reduction was not required in 85% of patients with SE or DE. Furthermore, $\leqslant$2% of events resulted in lapatinib discontinuation. The majority of events resolved (SE: 72% of patients; DE: 89% of patients). Diarrhea was managed in approximately 30% of patients using standard antidiarrhea medications (loperamide and Lomotil) and, in more severe cases, with hydration, octreotide and antibiotics.
Conclusion: This analysis demonstrates that most SE and DE related to lapatinib are low grade and infrequently require discontinuation or dose modification. Severe cases of DE are rare, and DE generally respond to standard interventions. For successful management of DE, proactive monitoring is crucial. Skin events are generally mild or moderate in severity and appear to differ clinically from those associated with other single ErbB1 tyrosine kinase inhibitors.