

98

Poster

The relative dose-intensity and new targeted therapies in breast cancer patients. Facts and hypotheses

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Background: Studies have shown that suboptimal relative dose-intensity (RDI) leads to poorer outcomes in breast cancer patients treated with standard chemotherapy in adjuvant setting. Evidence confirms that maintaining RDI more than 85% increases disease-free and overall survival. Some new targeted therapies are administered weekly or every two weeks. Such regimens based on a short time interval between consecutive cycles could be vulnerable in terms of RDI. It seems that tyrosine-kinase, VEGF and HER2neu inhibitors are the most exposed at that risk.

Material and Methods: The main goal of interest was to study the percentage of RDI reduction for some drugs with different time interval between cycles. As a general approach, for the same dose-intensity, regimens differ, being more "dense" or more "intense". By example, sunitinib 50 mg total daily dose, day 1 to 28, followed by two weeks interruption (the "on-off" concept), has the same dose-intensity as 37.5 mg continuously for six weeks. What is the most suitable schedule for a particular patient? No prospective randomised studies were performed to demonstrate potential survival differences between both approaches.

The time interval between consecutive cycles of treatment is specific for each targeted drug as follows:

7 days: Trastuzumab, Temsirolimus, Rituximab, Cetuximab, Alemtuzumab

14 days: Bevacizumab, Panitumumab

28 days: Temozolomide

42 days: Sunitinib

Results: As previously shown, the dose delay between consecutive cycles of treatment is the "dominant" covariate, being responsible of almost 60% of the total RDI reduction (E. Banu, 11th International Conference on Primary Therapy of Early Breast Cancer, 12 March 2009, St. Gallen:0076). The overall impact of dose delay on the RDI is more important for schedules based on 7 or 14-day interval compared with those based on 21 or 28-day interval, as specified in Table. By example, the impact of one day delay on the RDI is four times higher (3% vs. 12% RDI reduction) for a one-week schedule compared with one-month interval. Dose delay will be associated with a lower concentration at the end of the therapeutic window, the "plateau" of serum concentration could disappear and a new steady-state situation could be difficult to reach.

Table

Interval between consecutive cycles (days)	RDI reduction (%)			
	delay 1 day	delay 2 days	delay 3 days	delay 4 days
7	12	22	30	36
14	7	12	18	22
21	5	9	13	16
28	3	7	10	12
42	2	5	7	9

Conclusions: A longer tumour exposure by a "dense" and less "intense" regimen could potentially select some multiresistant clones, source of disease progression. Moreover, an "intense" and less "dense" regimen could be associated with important toxicities, especially haematological. We recommend as a general rule to avoid unnecessary delay between cycles, (including scheduling, patient or office-related). The expected outcome for those patients carrying chemo-sensitive tumours as breast cancer could be ameliorated following this rule, especially for patients treated with new agents as bevacizumab or trastuzumab (with chemotherapy or alone).

99

Poster

Concurrent whole brain radiotherapy (WBRT) and trastuzumab (T) in breast cancer (BC) patients presenting with brain metastases

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Background: Brain metastases are frequently encountered in patients (pts.) with metastatic Her2+ve breast cancer treated with T. It is not clear however, if T can be safely pursued during whole brain radiation therapy (WBRT). This study was aimed at evaluating the tolerance and response rates of WBRT and T given concurrently for brain metastases.

Material and Methods: Thirty-one Her2 positive metastatic breast cancer patients receiving WBRT for brain metastases and continuing on T (weekly or every 3 weeks) were identified. WBRT delivered a total dose of 30 Gy in 10 fractions in most pts. All pts were seen weekly to assess the treatment tolerance. All patients continued T after WBRT.

Results: The median follow-up was 23 months (2-66). All but 4 pts were presented with multiple brain metastases. The median age was 51 years (36-65) at diagnosis of BC, and 53 years (38-73) at diagnosis of brain metastases. Thirteen pts (42%) received concurrent chemotherapy in addition to T-WBRT. Median time to progression (TTP) from radiotherapy of brain metastases was 10.5 months. A complete response (CR) of all clinical symptoms was observed in 22 pts (71%); 6 had a partial remission (PR), 2 had stable disease (SD) and 1 progressed. Radiologically, there were 6 CR (19.3%), 17 PR, 8 SD. Median survival was 23 months (2-66+). Treatment was well tolerated with no early toxicity in 77% of cases (n=24); 7 pts presented with grade I-II nausea, asthenia or headache during WBRT-T. No grade III-IV symptoms were observed.

Conclusion: These results suggest that the continuation of T delivery during WBRT for brain metastases is well tolerated. Response rates of the combination of WBRT and T are encouraging. Prospective studies are needed to evaluate more precisely if the addition of T to WBRT adds a significant benefit to WBRT alone.

100

Poster

Angiosarcoma of the breast and vascular endothelial growth factor receptor

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Background: Breast angiosarcoma is rare and often associated with previous breast cancer treatment. This study aimed to define long-term outcomes in relation to common prognostic factors. The expression of vascular endothelial growth factor receptor (VEGFR) was also evaluated as it may be a potential target for anti-angiogenic therapy.

Patients and Methods: We retrospectively assessed outcomes in relation to age, association with previous breast-conserving treatment for breast cancer, tumour size, and grade in 19 patients without metastases at diagnosis. VEGFR was also assessed.

Results: Median follow up was 33 months (range 1-121). There were 6 local recurrences and 6 deaths for disease progression. Five-year disease-free survival and overall survival were high at 53% (95% confidence interval (CI), 20-86%) and 49% (95% CI 14-84%), respectively. No factor significantly affected survival. VEGFR was positive in 50% of cases and was more frequent in better differentiated cancer.

Conclusions: The association of VEGFR with G1/G2 tumours suggests the need for further investigations. We propose a multimodal therapeutic approach to this aggressive disease, our findings provide a biological rationale to consider anti-angiogenic treatment in VEGFR-positive cases.

101

Poster

STRIDE: phase III study of therapeutic cancer vaccine L-BLP25 with hormonal treatment as first-line therapy for women with hormone receptor-positive, inoperable, locally advanced, recurrent, or metastatic breast cancer

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Background: L-BLP25 (Stimuvax®; BLP25 liposome vaccine) is a therapeutic cancer vaccine that targets the MUC1 glycoprotein. MUC1 is overexpressed, and exhibits altered glycosylation, in many tumor types, including breast cancer (BC) and non-small cell lung cancer (NSCLC). High levels of soluble MUC1 (CA15-3) in the serum predict poor prognosis in BC. In previous studies, L-BLP25 has demonstrated an acceptable tolerability profile and a clear trend to extension of survival in patients (pts) with stage IIIB locoregional NSCLC. **STRIDE** (STimulating immune

Response In aDvanced brEast cancer) is a global randomized double-blind placebo-controlled phase III study assessing the efficacy and safety of L-BLP25 in combination with hormonal treatment as first-line therapy for postmenopausal women with hormone receptor-positive, advanced BC. Here we present the design of the STRIDE study.

Methods: Eligible pts are postmenopausal women aged ≥ 18 years with estrogen and/or progesterone receptor-positive, inoperable (by RECIST criteria) locally advanced, recurrent, or metastatic BC. They have HER2-negative disease and express ≥ 1 of the following five HLA haplotypes: HLA-A2, -A3, -A11, -B7, or -B35. Accrual into the study is ongoing with a target of 909 pts to be recruited by approximately 180 sites in around 30 countries worldwide. In addition to receiving standard hormonal treatment (tamoxifen, anastrozole or letrozole), pts are randomized 2:1 to receive either 1000 μ g L-BLP25 or placebo. Pts receive weekly subcutaneous vaccinations for 8 weeks, followed by maintenance vaccinations every 6 weeks until disease progression. Patients are stratified by disease stage, concomitant use of tamoxifen vs aromatase inhibitors, and exposure to prior adjuvant hormonal treatment. The primary endpoint is progression-free survival (PFS) time; secondary endpoints include overall survival time, objective tumor response, safety/tolerability, and quality of life. Exploratory biologic analyses are planned.

Results: The final analyses of PFS time and secondary efficacy endpoints will be conducted using data obtained when more than 586 progression-defining events have occurred in the study population.

Conclusions: The STRIDE study will investigate whether vaccination with L-BLP25 can extend PFS time in pts treated with hormonal therapy as first line therapy, who have inoperable, locally advanced, recurrent or metastatic BC.

Wednesday, 24 March 2010 18:15–19:15

POSTER SESSION

Targeting and profiling predictive and prognostic factors

102

Poster discussion

How the 70-gene tumour expression profile “MammaPrint” can assist in St Gallen 2009 treatment recommendations in 12 Italian hospitals

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Background: A microarray-based 70-gene tumor expression profile “MammaPrint” was established as a powerful predictor of disease outcome in breast cancer. The St Gallen 2009 recommendations include gene-expression signatures as an indicator for adjuvant therapy. Here we determined in a prospectively assessed Italian cohort how the 70-gene profile can assist in patient management.

Methods: MammaPrint was determined on 524 samples submitted in 2008 and 2009, from breast cancer patients (clinical T1–4N0–3M0) aged 26 to 98 years (median age 62 years). Fresh tumor samples were prospectively collected in 12 Italian hospitals by core needle biopsy or from a surgical specimen (study protocol MP 090). We assessed agreement between the treatment advice as recommended by the 2009 St Gallen Highlights and classification according to the 70-gene MammaPrint profile.

Results: According to the St Gallen 2009 treatment recommendations, 17 patients could forego any adjuvant treatment (<1 cm, LN0, PVI 0). Of these patients, 9 (53%) were classified to be poor prognosis signature by MammaPrint. The 84 Her2+ patients would be recommended anti-HER2 treatment as well as adjuvant chemotherapy according to the 2009 recommendations. Of these patients, 11 (13%) were classified as good prognosis signature by MammaPrint. All 43 (ER-) patients who are

recommended chemotherapy alone are classified as poor prognosis by MammaPrint. For the 380 ER+, HER2- patients, 9 would be recommended no adjuvant chemotherapy (Grade I and LN0 and 2 cm and ER $>50\%$) and 199 would be recommended adjuvant chemotherapy being either Grade III, or ≥ 4 LN, or >5 cm, or ER $<50\%$. Of these 199 patients, 60 (30%) are classified as low risk by MammaPrint. The remaining 172 ER+, HER2- patients fall in the subgroup for which St Gallen 2009 states that they have characteristics that are not useful for decision making; MammaPrint classified 102 (59%) as poor prognosis and 70 (41%) as good prognosis. Clinical data collection for an additional 364 patients is pending.

Conclusion: Widespread use of the MammaPrint prognosis signature has been accomplished in Italian community hospitals. For the majority of patients (90%) the St Gallen Highlights 2009 either recommend or suggest considering treatment with cytotoxic adjuvant therapy for whom MammaPrint indicates a low risk of recurrence in 31% of cases, potentially sparing patients from adverse effects.

103

Poster discussion

Socioeconomic differences in breast cancer tumour size and relative survival in the Netherlands

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Background: Breast cancer is the most commonly diagnosed cancer among females in developed countries. Despite improvement in survival over the last years, socially deprived females with breast cancer seem to have a decreased survival; usually due to a higher stage of disease at diagnosis. Aim of this study was to assess differences in T-stage and survival according to socioeconomic status (SES) for females with breast cancer in the Netherlands.

Methods: All females diagnosed with breast cancer between 1995 and 2005 in the Netherlands were selected from the Netherlands Cancer Registry. Patients were linked to the database of the Netherlands Institute for Social Research which keeps record of the SES according to postal code. A multivariable logistic regression was used to assess factors associated with SES. Overall Survival (OS) and Relative Survival (RS) were calculated where RS was calculated as the ratio between the survival observed and the survival that would have been expected based on the corresponding general population.

Results: Overall, 127599 patients were included. There was an association between SES and T-stage at diagnosis ($p < 0.0001$) after adjusting for histology, grade, N-stage and M-stage. Both OS and RS were associated with SES, with a decreased survival for the patients with a lower SES. Overall, 5-year OS was 80% for the high SES group and 75% for the low SES group (HR 1.4 (95% CI 1.3–1.5; $p < 0.001$) and RS was 87% versus 83% (RER 1.3 (1.2–1.4; $p < 0.001$). The socioeconomic differences remained statistically significant ($p < 0.001$) after adjustment for age, years, grade, TNM stage and surgical treatment.

Conclusion: Socioeconomic differences in T-stage and survival were observed in the Netherlands. The higher T-stage at diagnosis of patients with a lower SES only partly explains the decreased survival for females with breast cancer. To improve the decreased survival further research is needed to identify reasons for these socioeconomic disparities.

104

Poster discussion

Molecular biomarkers to predict neoadjuvant chemotherapy response in breast cancer patients treated with weekly paclitaxel plus carboplatin

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Background: Previously, we have reported the weekly PCb (Paclitaxel + Carboplatin) regimen in neoadjuvant chemotherapy (NCT) for breast cancer had a pCR rate of 19.4% (SABCS 2009, abstract 1099). However, there is lack of reliable marker to predict the efficacy of PCb. To identify molecular biomarkers and built different models including various markers to predict the efficacy and to evaluate whether including candidate molecular markers can improve the predictive accuracy of model for predicting response of weekly PCb NCT.

Materials and Methods: Retrospectively analyzed patients treated with weekly PCb (Paclitaxel 80 mg/m² and Carboplatin AUC=2, given day1, day8 and day15 out of every 4 weeks) NCT, routine clinical and pathological markers as well as pCR status were collected. Hormonal Receptor (HR)