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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).

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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 10fractions 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.

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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 rational to consider anti-angiogenic treatment in VEGFR-positive cases.

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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** (**ST**imulating immune