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Herceptin and Interleukin-12 combination therapy in patients with HER2/neu-overexpressing malignancies: a phase I trial

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We have observed that co-stimulation of natural killer (NK) cells with Interleukin-12 (IL-12) and Herceptin-coated Her2/neu-positive breast cancer cells leads to the secretion of large amounts of Interferon-gamma (IFN-g) and other potent immunomodulatory cytokines. We theorized that IL-12 would potentiate the anti-tumor actions of Herceptin and conducted an NCI-sponsored phase I trial using these two agents (T99-0032). Patients with metastatic Her2/neu-expressing malignancies (HER 1+, 2+, or 3+) received Herceptin on day 1 of each weekly cycle (4 mg/kg initially and 2 mg/kg thereafter). Beginning on week 3, patients also received intravenous injections of IL-12 on days 2 and 5. We have escalated the IL-12 component of this regimen within cohorts of three patients (30, 100, 300, or 500 ng/kg). Nine patients have been treated and those with stable disease or a clinical response at week 14 were allowed to continue therapy for one year. Seven patients had breast cancer, 1 had pancreatic cancer, and 1 had a neuroendocrine tumor. There has been one complete response in a patient with metastatic breast cancer (100 ng/kg dose level). A patient treated at the 300 ng/kg dose level experienced significant improvement in pain associated with widespread bony metastases, but progressed in L5 after 14 weeks and was removed from therapy. This regimen has been well tolerated with no reported Grade 3 or 4 toxicities. Fever, chills, and hypotension associated with IL-12 administration have been encountered, but have been easily managed. Correlative studies were conducted investigating cytokine levels and peripheral blood mononuclear cell (PBMC) activity in response to treatment. Of note, the only patient with measurable levels of serum IFN-g was the same one who experienced a complete clinical response. Analysis of this patient's PBMCs by Real-Time RT-PCR revealed an average 17-fold increase in IFN-g transcript. Intracellular cytokine staining showed significant production of IFN-g by both NK cells and T cells, whereas PBMCs of non-responders exhibited minimal production. Similar results were seen with levels of the anti-angiogenic factors IP-10 and MIG. These findings strongly suggest that immune modulation will enhance the anti-tumor efficacy of monoclonal antibody therapy.

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How much improvement in survival do early breast cancer patients require to consider endocrine therapy worthwhile?

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Purpose: Endocrine or hormonal therapies are increasingly used in the systemic treatment of early breast cancer. Each treatment intervention is begun in the belief that it will probably improve health more than it causes suffering, but trade-offs are often necessary. This study attempted to find out what trade-offs between quality and quantity of life are acceptable for patients

Methods: In this Patient Preference Interview (PPI) study, women who had previously taken part in a clinical trial of adjuvant endocrine therapy were asked (as part of a semi-structured interview) what minimum improvements in survival they would accept to balance their experience of endocrine therapy.

Results: The majority of the 84 women interviewed required an increase in survival time of an additional 3 and 5 years above expected survival without treatment (which would have been 5 or 15 years respectively). When considering 5-year survival rates respondents required an increase of 5% and 10% beyond expected 5-year survival rates of 80% or 60% respectively. These median acceptable benefits were higher than those in a similar study of adjuvant chemotherapy. There was some evidence to suggest that factors such as a longer duration of therapy and toxicity attributed to therapy influenced the required survival gains. Route of administration of treatment by tablets or injections had little influence on acceptable gains. Few respondents were willing to 'trade-of' any survival gains in order to avoid their worst side effect. Hypothetical survival rate questions had worse reliability than questions based on the individuals' expectations or choices made for a sister or best friend, which calls into question the validity of preference studies where 'trade-offs'are made on behalf of a hypothetical unknown person.

Conclusions: Patients were able to quantify the benefits which would make their treatment worthwhile, and such views should be considered when evaluating new treatments, as a bridge between survival and quality of life data.

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The ATAC (Arimidex™, Tamoxifen, Alone or in Combination) adjuvant breast cancer trial in postmenopausal (PM) patients (pts): Factors influencing the success of PT recruitment

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Purpose: The ATAC trial evaluates, in a randomized double-blind design, anastrozole (AN) alone or in combination with tamoxifen (TAM), relative to TAM alone as 5-year adjuvant treatment for PM pts with early breast cancer. To date, this trial is the largest adjuvant trial ever conducted in such pts. In approximately 30 months, the trial recruited over 9300 pts from 380 centres in 21 countries. A number of factors influencing the success of pt recruitment into this trial were highlighted in a questionnaire that was sent to all trialists.

Methods: This questionnaire included 11 statements rated for level of importance on a three-point scale.

Results: A total of 63% of the trialists returned the completed questionnaire. The top six motives for recruiting pts into the trial are included in the table.

	Very important (%)	Somewhat important (%)	Not important (%)
I found the scientific rationale of the trial attractive	84	15	1
I found the design easy to explain to the patients	79	18	3
Pragmatic design in line with standard practice	76	21	3
Infrastructure of the trial was well organised	70	26	4
The treatments were oral and relatively non toxic	69	28	3
Logical extension of earlier endocrine trials	67	29	4

Conclusions: Scientific rationale and pragmatism were leading reasons for inclusion of pts into the trial. A new questionnaire will solicit opinion from pt participants.

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Neoadjuvant chemotherapy with standard vs high dose of epirubicin plus filgrastim for locally advanced breast cancer. Report from the mexican oncology study group (MOSG)

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One research approach to improve the efficacy of tumor response and survival of patients with locally advanced breast cancer (LABC) is chemotherapy dose intensification. Purpose: Evaluate the response rate, toxicity and overall survival in 2 groups of LABC patients using different doses of Epirubicin as part of a FEC regimen. Inclusion criteria: naïve patients with LABC. All patients received 5-FU and Cyclophosphamide at 500 mg/m2 on day 1, and Epirubicin either 70 mg/mg2 (arm A) or 120 mg/mg2 (arm B) every 3 weeks. On arm A, G-CSF (Filgrastim) 5 μg/k/day was administered days 2-11 or until an ANC of 2,000 was obtained. Four cycles were followed by locorregional treatment Results: 236 patients were included from 02/98 until 03/01 (112 arm A and 124 arm B). Characteristics and results for arm A vs B were respectively: median age 45.4 vs 46.3 years; stage IIB 2% vs 5%, IIIA 48% vs 37%, III B 50% vs 58%; primary tumor 2 cm 3% vs 5%, 3 cm 56% vs 53%, 4 cm 34% vs 33%, > 5 cm 6% vs 9%; Karnofsky of 100%:

83% vs 72%; premenopausal 42% vs 43%. Delay on 2nd cycle delivery observed in 20% (5.6 days) vs 15% (3.62 days,p=0.7), on 3rd cycle 11% (5.3 days) vs 23% (7.8 days, p=0.04), on 4th cycle 9%(6 days) vs 23% (7.5 days, p=0.02); however need for dose reduction = cycle 2: 11% vs 4% (p=0.1), cycle 3: 11% vs 5% (p=0.2) and cycle 4: 13% vs 4% (p=0.06). Response rate for arm A vs arm B: CR 36% vs 38% (p=0.7), PR 39% vs 49% (p=0.1), SD 21% vs 5% (p=0.003). Toxicity: more than 75% of delivered cycles in both arms had Grade 0-2 neutropenia and thrombocytopenia: stomatitis and diarrhea were mild and similar in both arms, with only 6 events of grade 3 mucositis (one in arm A and 5 in arm B). Nausea and vomiting were reasonable controlled with setrones in all patients. Non cardiac event was informed. Hospitalization due to complications 4 pts vs 6 pts. Median follow up 20 months. Disease free survival 18.7 months vs 21.1 months (p=NS), median overall survival 19.9 months vs 20.7 months (p=NS). Conclusions: neoadjuvant FEC with high dose of Epirubicin compared with standard Epirubicin dose improves overall tumor response (87% vs 75%) but was not statistically different. Results on overall and disease free survival are also similar as far. Intensification of Epirubicin in FEC regimen with G-CSF support is feasible and safe, and a potential further benefit in overall and disease free survival can not be discharged with a longer follow up.

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Influence of systemic therapy on the persistence of occult metastatic cells in bone marrow of breast cancer patients

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Background: The presence of occult metastatic cells in bone marrow (BM) of breast cancer patients at the time of diagnosis indicates occult hematogenous tumor cell dissemination and increases the risk of subsequent distant disease. Currently, there are no data available on the influence of different adjuvant therapies on the survival of these cells.

Methods: We analyzed bone marrow aspirates of 161 patients without evidence of recurrenceat the time of primary diagnosis and a median interval of 13 months (range: 6 - 74) thereafter. Carcinoma cells were detected using a standardized immunoassay with monoclonal antibody A45-B/B3 directed against cytokeratin (CK).

Results: At the time of primary diagnosis, 46 of 161 patients (29%) had apositive BM finding. Of these, 45 (28%) had a positive BM finding at the time of the second BM analysis. Among those patients with an initially negative BM finding, 21 patients (13%) had a positive BM finding at the second aspiration, while 24 patients (15%) remained BM-positive. Of the 46 patients with ITC at the time of primary diagnosis, 23 patients (50%) received adjuvant chemotherapy, 7 patients (15%) received endocrine therapy and 16 (35%) patients had no systemic treatment at all. 56% of the patients without systemic therapy (n=7) converted to a negative BM status at time of follow-up examination, while 43% of the patients with endocrine (n=4) or cytostatic (n=13) therapy became negative (P= 0.70).

Conclusion: In a considerable number of patients with primary breast cancer, minimal residual disease can be detected by follow-up BM analysis. Independently of systemic therapy, about half the patients are remain BM-positive suggesting failure of therapy and risk of subsequent development of distant disease.

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Weekly high-dose paclitaxel(HD-P) has significant antitumor activity in inflammatory breast cancer (IBC)

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IBC is a rare but aggressive, often fatal form of breast cancer. Anthracycline-based regimens are the standard of treatment for IBC. The quality of response to induction chemotherapy (IC) still represents the most important prognostic factor. We have shown that the use of paclitaxel (225 mg/m2 given as 3hr IV infusion) in anthracycline-resistant IBC was associated with improved resectability that translated in a median survival of 46 months (95% C.I., 36 to 56 months) (submitted for publication).

Based on this premises a pilot study was designed to test the possibility to achieve a high pathological and/or clinical complete remission (CR) rate with an intense IC program before proceeding to local treatment. IC consisted of a sequential treatment with an anthracycline-based regimen (FAC) for 4 cycles, weekly HD-P (175 mg/m2 weekly x 6 consecutive weeks, 8-week cycle) for 2 cycles and, in case of chemotherapy-refractory disease, high-dose chemotherapy with peripheral blood stem cell support (HDC-PBSCS). Twenty patients (pts) were enrolled between 10/98 and 8/00; the median age was 52 years (range 34-63). One patient was ineligible, 19 pts were eligible. The median follow-up is 18 months (range 8-30). Eighteen pts have completed IC, 1 patient refused treatment. A clinical CR was achieved in 6/18 pts (34%). Three pts underwent HDC-PBSCS. Local treatment consisted of combined chemo-radiotherapy (weekly paclitaxel 50 mg/m2) for 3 pts, 11 of them underwent mastectomy and one refused surgery. Five of these 11 were found to have achieved a pathologic CR (5/11, 45%). Two patients have progressed; the median time-to progression (TTP) is 16+ months (range 10-22). Neurosensory and skin toxicity grade 3-4 were paclitaxel dose-related and required dose-modifications.

In conclusion, the use of sequential FAC-HD-P appears to be associated with a promising antitumor activity when used as IC in IBC.

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Hypofractionated and accelerated radiotherapy with amifostine cytoprotection (HypoARC) for high-risk breast cancer patients

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Purpose: Post-mastectomy radiotherapy in high risk breast cancer patients reduces the risk of local relapse by 20-30%. However, a 'wait and see'; policy is often adopted as surgical therapy alone is successful in up to 70% of mastectomized patients and 5-10% of patients will experience a recurrence of the disease despite radiotherapy. Establishment of short, still safe and effective RT regimens would render adjunctive radiotherapy more appealing. We evaluated the toxicity and the efficacy of a Hypofractionated and intensively Accelerated RT regimen supported with amifostine Cytoprotection (HypoARC) in a cohort of 72 high-risk breast cancer patients treated with modified mastectomy or conservative surgery and anthracycline based chemotherapy.

Patients and Methods: High-dose of amifostine, 1000mg, was given as a 5min iv infusion before each one of 12 consecutive fractions (f) of RT (3.5Gy/fraction x 4f and 4Gy/f x 8f; 1 f/day, 5 f/week). The breast or the chest-wall as well as the supraclavicular and axillary areas were included in the RT fields. The follow-up of patients ranges from 18-42 months (median 28).

Results: Ninety-two % of patients successfully completed the regimen, the only side effects being mild nausea and asthenia. In 7% of patients amifostine was interrupted because of a rash/fever reaction. A dramatic reduction of the acute skin toxicity was noted. Acute pneumonitis, as well as late toxicity from breast, chest-wall, axillary and lung tissues in the HypoARC regimen were lower, although not significantly, than the toxicity observed in two matched control cohorts treated with standard fractionation. Both HypoARC and standard RT significantly reduce the local relapse rate, while the distant metastasis-free and overall survival times remained unaffected. However, in cases with a high cancer cell proliferation index (MIB1), HypoARC was associated with a significantly better local control rate.

Conclusions: The HypoARC regimen is convenient for both the patients and the radiotherapy departments. The regimen is well tolerated and shows a significantly better profile in terms of early toxicity, while a reduced rate of late sequel may be expected. The overall local control rate is comparable to the expected from conventional RT. Translational studies are on-going to identify sub-groups of patients, where HypoARC may prove more effective than standard RT.