1321 PUBLICATION

Palliative chemotherapy with escalated single Ifosfamide dose in an ambulatory setting for patients with advanced breast cancer

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Ifosfamide has single drug activity of 47% in advanced breast cancer (ABC). For other tumors, a dose-dependent response rate is known. Data regarding the best monosubstance level for ABC is absent. Since Feb. 97, 28 pts with ABC, naive to palliative chemotherapy, received ambulatory Ifosfamide: starting dose 2.5–3 g/m^2 days 1–3 every 21 days. Dose was escalated for the following cycles 20%, if hematological toxicity and general tolerance were less than G-3. Mesna: i.v. 500–600 mg/m^2 at hour 0 + 4 and 1000–1200 mg/m^2 po at hr 8 + 14. Patients (pts): mean age 49 years old (24–63 y); stage IV 18 pts, relapse 9 pts, persistent IIIB one pt; site of metastasis: lymph node 19, bone 18, breast 17, lung 10, skin 4, liver 2, pleural, mediastinum and eye one each; performance status: mean ECOG 1; median DFI = 13.2 months.

Results: PR 20/28 pts (71%), SD 1 pt (4%) and Progression 7 pts (25%); 3 PR and 1 SD still under treatment. Subjective symptoms improvement when applicable: yes = 18 pts, no = 5 pts; number of Ifosfamide delivered cycles = 4.4 (1–6); maximal known response to Ifosfamide: at 1st cycle = 16 pts, 2nd = 2 pts, 3rd = 1 pt. Dose escalation possible in 22 pts, not performed in 6 pts (2: intolerance, one: omission, 3: progression). Escalation was possible at least to 9 g/m^2 per cycle and some cases even to 11.5, 12 and 15 g/m^2 without G-CSF. Non hematological toxicity: G-3 cystitis 1 pt; G-3 emesis 3 pts, mild muscular pain 10 pts; dizziness 4 pts; mesna oral taste intolerance 3 pts; unexplained oedema 2 pts.

Conclusions: 1. Ambulatory high dose Ifosfamide monotherapy is feasible, with OR of 71% 2. Response rate shows to be early (65% at 1–2 cycle) and symptoms relief good: 18/23 pts. 3. Escalation at least to 9 g/m^2 was feasible and safe in 22/25 pts. As a single drug, Ifosfamide has a related dose-response in ABC. Combination with other drugs, deserve Ifosfamide dose level maintenance.

1322 PUBLICATION

Immunologic approaches for breast cancer patients in the setting of stem cell transplantation

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As cure rate in breast cancer (BC) is still limited there is a need for new therapeutic approaches. We have previously demonstrated improved survival and disease free survival in patients with leukemia and lymphoma by using immunologic approaches including cytokines, growth factors and donor lymphocyte infusions post autologous stem cell transplantation (ASCT). We therefore hypothesized that this approach may be of value for patients with BC. Twelve BC pts received s.c. rhGM-CSF (2.5 mcg/kg) X3/w for 3 months post ASCT (group 1) as rhGM-CSF have been shown to potentiate anti BC tumorogenicity in both cell line and animal models through activation of monocytes, dendritic cells, TNF production and antigen presentation. Twelve other patients served as control (group 2) and received GM-CSF for a short period (up to engraftement). Seven other patients were treated with allogeneic stem cell therapy (group 3). The conditioning regimen included carbopatin, thiotepa, etoposide and melphalan for group's 1 + 2 and cyclophosphamide/fludarabine and ATG for group 3. GM-CSF administration resulted in moderate toxicity including fever and rash in 4 patients both in the study and the control groups. No difference in survival and disease free survival was observed in group 1 and 2. Out of 7 patients that received allogeneic cell therapy 5 patients developed graft versus host disease. In summary cytokines and cell mediated immunotherapy should be further evaluated in breast cancer patients as attempts to improve therapeutic options in this cohort of patients are mandatory.

1323 PUBLICATION

Vinorelbine and farmorubicin as neoadjuvant chemotherapy in locally advanced breast cancer

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Purpose: The combination of vinorelbine and farmorubicin proved to be highly effective in metastatic breast cancer. In a prospective study, we evaluated vinorelbine and farmorubicin as neoadjuvant chemotherapy (NCT) in stage 3 A and B breast cancer.

Patients and Methods: Between March 1997 and March 1999, 53 consecutive patients with locally advanced breast cancer were entered into the trial. The median age was 37 (24–66 years), median tumor size was 8 cm. Patients were submitted to 3 cycles of NCT. The regimen consisted of vinorelbine (25 mg/m^2 IV infusion d 1 and 5), and farmorubicin (40 mg/m^2 IV d1 and 5) every 21 days. Patients were then submitted to modified radical mastectomy followed by ER (45 cGy/4 weeks). The treatment was completed by another 3 cycles of chemotherapy followed by tamoxifen in cases having tumors with positive hormone receptors.

Results: After a median follow up of 8 months, 3/53 (5.5%) achieved CR and 45/53 (85%) patients had PR. Two patients had SD (3.8%) while 3 cases (5.7%) had PD. Following Chemotherapy, 38 cases (72%) were subjected to Surgery. Patients received 232 cycles, the median number of courses per patient was 5 (range 2–6). Up till now, 11 patients (21%) relapsed. Toxicity: Leucopenia grade 3 and 4 was encountered in 15 cases (28%), alopecia in 50 cases (94%), Phlebitis in 35/53 (66%) and neurotoxicity in 20 cases (38%).

Conclusion: The combination of vinorelbine and farmorubicin is an effective regimen when used as NCT in locally advanced breast cancer with acceptable toxicity.

1324 PUBLICATION

Taxotere® (T) and doxorubicin (D) combination: A phase II South American study in first line treatment (tt) of metastatic breast cancer (MBC)

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T and D are the most active single agents used in the tt of MBC. D has long been considered as a standard and T has demonstrated a superior antitumor activity in a phase III trial (Chan et al., SABCS 97). When combined, high response rates have been observed. A confirmatory phase II study was undertaken in Chili, Colombia, Ecuador, Peru, Mexico and Venezuela. D was administered at 50 mg/m^2 (d 1 i.v. bolus) followed 1 hour later by T 75 mg/m^2 q 3 wks for 6 cycles followed, for responders, by 3 cycles of T alone at 100 mg/m^2. 3 days oral premedication with 8 mg bid dexamethasone was given. The main eligibility criteria were: proven locally advanced or MBC, age < 65, PS ≤ 2, no prior chemotherapy (CT). For adjuvant or neoadjuvant at least 12 months interval between the end of CT and first relapse. 80 pts have been treated and the results are presented on 33 pts. The main characteristics are: median age 48 years (26–65), 94% PS 0–1, median organ involved 2 (1–6), 52% with visceral involvement, 187 cycles have been administered with 186 at full dose. Preliminary overall RR is 69.6% with 13% of complete response. Neutropenia (per pt) grade 3/4: 75%, febrile neutropenia 18%, 6% of cycle. No G 3/4 infection has been reported. Full data will be presented at the meeting.

1325 PUBLICATION

A phase I study of docetaxel (D) in combination with high dose cyclophosphamide (C) as first line chemotherapy in patients (pts) with metastatic breast carcinoma (MBC)

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There is a need for development of combination of new drugs such as D with non-anthracycline classical ones such as C. This ongoing study explores the feasibility of DC combination administered every 2 weeks in previously untreated pts for MBC, without G-CSF prophylactic support. Eligible pts have a progressive MBC, no prior chemotherapy for metastatic disease, no prior taxanes, age ≥ 18 and ≤ 65 years, WHO PS ≤ 2. To date, 35 pts have

been included and we report the safety results on 29 patients enrolled in the first 5 dose levels:

C/D (mg/m^2)	Nb of pts	Nb of eval. cycles (cy)	Neutropenia G4 (% cy)	Febrile neutropenia (% cy)	Non-hematol. toxicity G3 except alopecia (% cy)
1000/60	6	36	80.5	8.3	0
1000/66	7	38	57.8	10.5	10.5
1200/66	7	42	61.9	4.7	14.2
1000/75	6	33	69.6	6.0	9.0
1200/75	3	13	92.3	0	15.3

No grade 4 non-hematological toxicity was reported. The maximum tolerated dose is not yet reached. Regarding the efficacy results from 24 evaluable pts, 14 pts responded (1 CR and 13 PR), 9 were in stable disease and 1 pt progressed during the treatment. We are continuing to explore the dose level D 75 mg/m^2 and C 1200 mg/m^2. Antitumoral efficacy of this combination is encouraging (ORR = 58%).

1326 PUBLICATION

The responsivness of bone metastases in breast cancer patients to radiotherapy: Prospective study comparing six different fractionation schedules

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Aim: The aim of this paper was assesment of values of different regimens of radiotherapy fractionation, determining radiologically assessed response, as well as analysis of effect of further evolution of the disease with impact on quality of life and on overall survival.

Materials and Methods: Prospective nonrandomised clinical trial was performed during the period: 1.1988.–12.1996., in the Institute for oncology and radiology of Serbia (Belgrade, Yugoslavia), to evaluate the effectivness of six different radiotherapy schedules of bone metastases irradiation. Thise schedules were: (A) short – 14 Gy/2 fractions, 48 hours interval between them and 16 Gy/4 fractions; (B) median 18 – Gy/6 fractions and 20 Gy/8 fractions; and (C) long ones – 30 Gy/10 fractions and 40 Gy/20 fractions. A total of 386 patients (441 irradaiated lesions) with breast cancer and osteolytic bone metastases as a first and sole relaps of the disease, were included in this trial. The responese quality was evaluated radiographicaly, 2 and 4 months after completition of irradiation.

Results: Looking at the relation between response rate and subjection to treatment arms A, B and C no statistical differences were notable. For short and median irradaition regimens better response is achived at the second than at the first radiological control. The probability of five years survival of patients with bone metastases and first and sole relaps was 45.01%, with median overall survival of 31 months. Response quality to undertaken treatment by irradaition is not predictor of overall survival.

Conclusion: It is concluded hat short fractionation radiotherapy regimens is as effective as median and long ones in palliation of bone metastases in breast cancer patients with this form of metastatic disease.

1327 PUBLICATION

Improved survival for patients with metastatic breast cancer treated with high dose chemotherapy compared with matched controls who received conventional treatment

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We have examined the survival of 2 groups of patients with metastatic breast cancer who were treated between 1988 and 1997; one group had conventional anthracycline combination chemotherapy and the other high dose (HDC) as first line treatment. The study was performed to test Rahman's hypothesis (ASCO 1995) that selection of patients largely explains the survival (S) benefit claimed for HDC in non-randomised studies. This study has matched the presenting characteristics of patients treated with conventional therapy (Conv.) against those of a series of 50 patients treated with HDC. For this study patients with non-visceral metastases were excluded. HDC comprised cyclophosphamide 4 gr/m^2 followed by GCSF/PBSC harvesting then melphalan 140 mg/m^2 plus thiotepa 600 mg/m^2.

Characteristics: HDC: n = 48, Age 41 [27–56], ECOG 1 [0–4], DFI 86 wk [0–240] Conv: n = 190, Age 48 [28–57], ECOG 1[0–4], DFI 94 wk [0–684]

Results: (No treatment associated mortality for HDC) HDC: Median S 24 mo [7–116]; 1, 3, 5 yr S 81%, 27%, 15% Conv.: Median S 15 mo [0–89]; 1, 3, 5 yr S 53%, 13%, 2.6%

The HDC results are similar to those reported by us and others earlier. The Conv. results are at least as good as the outcomes reported elsewhere. The study suggests that the benefit of HDC in this group of patients with visceral mets is not entirely explained by patient selection.

Haematological malignancies

1328 ORAL

Genes and rearrangements in 3q21 relevant to leukemia

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Rearrangements of the long arm of human chromosome 3, in particular of bands 3q21 and 3q26, are well documented in leukemia. In 3q26 the EVI1 gene, a zinc finger transcription factor not normally expressed in hematopoietic tissues, has been implicated, but the role od sequences in 3q21 remains poorly understood. The breakpoints within 3q21 are clustered within a 30 kb region which appears to be extremely gene rich as we previously identified up to nine novel genes in an 80 kb P1 clone that spans 10 different breakpoints& These putative genes are of unknown function, are generally expressed at low levels in normal tissues and in a set of cancer cell lines, and breakpoints are dispersed among them. Most recently, examination of a leukemia derived cell line and nine patient samples carrying t(3;3)(q21;q26) and inv(3)(q21;q26) has demonstrated activation of expression of some of these genes. In addition, some activated genes are involved in complex alternative and/or intergenic splicing. For example, formation of a fusion transcript between the 3q21 gene Ribophorin I and the 3q26 gene EVI1 is a common event in t(3;3)(q21;q26) observed both in s leukemic cell line and in several patients. Fusion between the 3q21 gene GR6 and EVI1 has been more rarely observed, and reflects a less common 3q21 breakpoint location. Each of these fusions splice the 5'-end of the 3q21 gene into exon 2 of the EVI1 gene, altering the translational start site and potentially producing EVI1 proteins with altered transcriptional activator properties. These data suggest that sequences in 3q21 play a role in leukemia development or progression.

1329 ORAL

DNA fingerprinting of low-grade extranodal marginal zone B-cell lymphoma (of MALT type)

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Introduction: DNA amplification by PCR with primers designed on the widely distributed Alu sequences allows the production of specific inter Alu DNA-fingerprints. Amplification of tumour and matched normal DNA can show differences due to genetic alterations within tumour genome. Thus, molecular events responsible for the malignant growth pattern might be identified. We applied this approach to study low-grade extranodal marginal zone B-cell lymphoma (of MALT type).

Methods: DNA was extracted from frozen MALT lymphoma and from matched peripheral blood samples. After separate digestion with 2 restriction enzymes, DNA samples were amplified by PCR with 3 different primers. A comparison between the fingerprint pattern for lymphoma and Pb samples was made. Inter-Alu (ITA) bands differing between the two samples were excised from the gel, cloned and sequenced. The obtained DNA sequences were analysed for homologies in the GenBank database, using the BLAST software.

Results: Six cases of low-grade MALT-lymphomas have been already analysed. 17 differing bands (range 400–800 bp) were excised from gels. Nine bands were absent in the tumour, 7 in the Pb, and 1 appeared apparently amplified in the lymphoma sample. The combination of ALU-I restriction enzyme and ALU-IV primer was the most informative. DNA sequences analysis showed highly significant homologies for three ITA bands (with chromosome 9p21, chromosome 22q11, and chromosome 16p12). Additional cases are going to be studied.