and doxorubicin or paclitaxel and navelbine. Two weeks later accelerated radiotherapy was begun. The breast and internal mammary chain were irradiated with two tangential fields, nodes – with anterior irregulary shaped field. Linear accelerator (6 MeV) was used to deliver 2 Gy per fraction, b.i.d., for 5 days/week up to a total dose of 44 Gy to breast and 40 Gy to regional lymphatic nodes. Radical mastectomy was performed after three-four weeks rest period.
Results: The overall objective preoperative response rate was 93.5%. When the postmastectomy histopathological examination was performed, there was no evidence of primary tumour in five (16%) cases. There were found only devitalized single tumour cells in 7 (22.5%) postmastectomy breasts, and another five speciments presented significant tumour destruction. In 12 (48%) patients of 25 with initially involved lymphatic areas, the nodes turned out to be morphologically intact. There were no serious reactions and toxicity during and after treatment. In 5 cases we observed delayed healing of postoperative wound. Indurative subcutaneus fibrosis occurred in 3 womens. During the follow-up period there were 4 (12.9%) deaths due to disease progression.
Conclusion: Accelerated preoperative irradiation in combination with chemotherapy is effective treatment of breast cancer. Our technique allows performing mastectomy and adjuvant chemotherapy without a significant delay. Overall time of radiation treatment was only 15 days. This regimen proved to be safe with accepted toxicities. It seems to be reasonable not to replace preoperative irradiation by chemotherapy but to combine these treatment modalities.

473 PUBLICATION

High-dose chemotherapy and autologous peripheral blood stem cell transplantation in metastatic breast cancer. Updated results of a single center

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Introduction: High-dose chemotherapy is not standard in the treatment of breast cancer, neither in the adjuvant nor in the metastatic setting. In this retrospective study, we aimed to review the interim data of metastatic breast cancer patients who underwent high-dose chemotherapy (HDC) and autologous peripheral blood stem cell transplantation (APBSCT) in our BMT center.
Material and methods: Between October 1984 and March 1997, 28 patients with metastatic breast cancer were treated with HDC and APBSCT. Their ages ranged from 23 to 63 years with a median age of 35 years. The time from diagnosis to transplant ranged from 109 to 2470 days with a median of 717 days. The number of their previous chemotherapy cycles ranged from 4 to 18 with a mean of 9. Their preparative regimens were: CNV (n = 19): Cyclophosphamide 2.4 g/m^2, mitoxantrone 35 mg/m^2, etoposide 250 mg/m^2/d *6 days; ICE (n = 8): Ifosfamide 2.5 g/m^2/d *6 days, carboplatin 250 mg/m^2/d *6 days, etoposide 250 mg/m^2/d *6 days; CNP (n = 1): Cyclophosphamide 60 mg/kg/d *2days, mitoxantrone 35 mg/m^2, carboplatin 200 mg/m^2/d *6 days. In the posttransplant period, 20 patients received G-CSF (granulocyte colony stimulating factor), 6 patients GM-CSF (granulocyte-monocyte colony stimulating factor), and 2 patients received no GF.
Results: Recovery to $\geqslant 1 \times 10^9$ leukocyte/L occurred at a median of 11 days, platelet recovery to $\geqslant 20 \times 10^9$/L was 13 days. A mean of 3.3 units of red cell suspensions and a mean of 2.8 units of platelet suspension were transfused. The mean hospitalization duration was 13 days. After median follow-up of 1010 days (range 3–2921 days), the survival probability at five years was calculated as 25%. The transplant related mortality was 10.3%.
Conclusion: The place of HDC in metastatic breast cancer is still controversial. Further randomized studies with more patients and longer follow-up are needed to clarify this issue.

474 PUBLICATION

Efficiency of Toremifen and Letrozol in the treatment of patients with advanced breast cancer

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Background: For the last years the discussion and researches about efficiency and sequence of use of antiestrogens and aromatase inhibitors in the treatment of advanced breast cancer have not been stopping. For many years antiestrogens (Tamoxifen and Toremifen) were considered standard medicines of first line in the treatment of postmenopausal women with advanced breast cancer. Last years results of researches which have demonstrated advantages aromatase inhibitor Letrozol over Tamoxifen as first line therapy at the patients with advanced breast cancer were published. At the same time did not investigate comparative efficiency high doses of Toremifen and Letrozol. The aim of this trial is comparative study of Toremifen and Letrozol efficiency in the treatment of patients with advanced breast cancer.
Material and methods: 451 receptor statuses not considered patients with advanced breast cancer were involved in this clinical trial. Patient were divided on 4 groups/Hormonal therapy with Tamoxifen at a dose of 20 mg once daily was administered in 117 patients – I group, hormonal therapy with Toremifen at a dose of 60 mg once daily was administered in 115 patients – II group, 106 patients (III group) received Toremifene at a dose of 240 mg daily, 113 patients (IV group) were treated with Letrozol at a dose of 2.5 mg once daily. Patients continued on study medication until disease progression. Efficiency of treatment was determined with following criteria: objective effect, side effects and duration of remission.
Results: In the first group 30(25.6%) patients, in second group 38 (33.0%) patients, in the third group 44 (41.5%) patients, in the fourth group 40 (35.4%) had objective effect. Median remission time of 9.2; 11.3; 14.5 and 13.1 months. Side effects in all groups were not significant, did not require specific correction and delay of the treatment.
Conclusions: Our data indicated about advantages of Toremifen compared to Tamoxifen and comparable efficiency compared to Letrozol. On the base of the data we can recommend Toremifen for wide use as first line hormone therapy of patients with advanced breast cancer.

475 PUBLICATION

Clinical experience with trastuzumab in metastatic breast cancer

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Background: Trastuzumab (Tmab) is a monoclonal antibody used in the treatment of metastatic breast cancer (MBC) overexpressing c-erbB2 where it has been shown to improve time to progression, duration of response to chemotherapy and survival time.
Material and methods: We conducted a retrospective cohort analysis of patients (pts) with MBC overexpressing c-erbB2 (imunohistochemestry (IHC) 3+ score or positive FISH staining) treated with Tmab between Jun 2001 and Dec 2004 in Oporto's Instituto Português de Oncologia. Data was collected on demographics, tumour histology and stage, type and timing of all treatments offered as well as data on Tmab use. Outcome measures were time to progression (TtP) and survival after initiation of Tmab therapy. Statistical analysis was performed with SPSS 12.0.
Results: Fifty three pts were treated with Tmab. Their mean age at breast cancer (BC) diagnosis was 47.3 years (SD = 10). Initial stage grouping were: stage I in 6 pts, stage II in 10 pts, stage III in 30 pts and 7 had metastatic disease. Ductal invasive carcinoma was present in 49 (92.5%) pts, micropapilary carcinoma in 3 pts (5.7%) and 1 pts had carcinoma with no other specification. Positive estrogen receptor (ER) was present in 35 pts (67%) and 23 (44%) had positive progesterone receptor (PR). c-erbB2 overexpression was determined by IHC in 47 pts (89%) and by positive FISH in 6 pts (11%).
Radical mastectomy was the first treatment of 23 pts (43%), lumpectomy in 12 pts (24%) and chemotherapy was the initial treatment of 18 pts (33%). On the first relapse, 25 pts (48%) were treated with chemotherapy and Tmab was a first line palliative treatment in 19 pts (39%). Twenty-three patients developed minor side effects and only one patient had to stop Tmab because of cardiotoxicity.
Follow up was complete for all pts. Overall mortality was 46% (n = 23). The median survival time was 20 months. Survival was worse when pts had negative PR (p = 0.01 Log Rank [LR]) and age > 50 at BC diagnosis (p = 0.004 LR). The median TtP after initiation of Tmab was 10 months. PR negative pts (p = 0.045 LR), age at BC diagnosis > 50 (p = 0.004 LR) had a significative lower median TtP. We found no association between ER status or histologic grade and survival or TtP.
Conclusions: Tmab was an active and well tolerated drug in women with MBC and c-erB2 overexpression. In our series PR status and younger age a BC diagnosis were surrogate markers of improved response to Tmab therapy.

476 PUBLICATION

Weekly Docetaxel seems to be as effective but better tolerated than 3 weeks Docetaxel

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Considering the fact that weekly Paclitaxel was demonstrated to be as effective but less toxic than 3 weekly Paclitaxel, we evaluated the same

parameters for 30 patients (p) with metastatic breast cancer (MBC) for which they got docetaxel-based chemotherapy in our clinic (september 2004-may 2005).
Docetaxel 25 mg/m, day 1, 8, 15 was associated to Epirubicin 60 mg/m^2 day 1 (23 p), to 5 Fluorouracil 450 mg/m, day 1, 8 (2 p) or to Carboplatin AUC6 day 1 (5 p) and the cycles were repeated every 21 days.
All patients were evaluated after 4 cycles of therapy. Response rate was 86.6% (26 p) (4p had disease progresion). Common secondary effects were: neutropenia (grade 3; only 1p, after cycle 4, grade 2; 8p, after cycle 3, grade 1; 12p, during chemotherapy), mucositis (grade 2; 3p after cycle 2, 4p after cycle 3, 3p after cycle 4, grade 1; 20p during chemotherapy), nausea (grade 2; 8p after cycle 1, 9p after cycle 2, 7p after cycle 3 and 7p after cycle 4) and fatigue (grade 3; 1p after cycle 1, 1p after cycle 2, 2p after cycle 3, 2p after cycle 4, grade 2; 15p after cycle 1, 14p after cycle 2, 20p after cycle 3, 21p after cycle 4). All toxicities were corrected by supportive means, none was life threatening.
Comparing our results to the published data on Docetaxel 3 weekly chemotherapy we consider the weekly Docetaxel schedule highly effective and better tolerated with one exception: fatigue, that is obviously worse for Docetaxel weekly schedules than for 3 weekly schedules, but manageable with regular supportive means.

477 PUBLICATION

Preliminary results of a Phase II study of neoadjuvant treatment with docetaxel (T), doxorubicin (A) and capecitabine (X) in locally advanced or inflammatory breast cancer

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Background: Previous studies suggest that combined treatment of chemotherapy+surgery+radiotherapy has a high survival rate in patients with locally advanced or inflammatory breast cancer. Primary objective was evaluate response rate. Secondary objectives were time to progression and toxicity profile of neoadjuvant chemotherapy T, A and X in patients with locally advanced or inflammatory breast cancer.
Patients and methods: Eligibility criteria: Patients with histological confirmation of locally advanced or inflammatory breast cancer, ECOG PS $\leqslant$ 2, age $\leqslant$ 75 years and LVEF >50%, adequate bone marrow, renal and hepatic function. Prior systemic therapy, surgery or radiotherapy for breast cancer was not allowed. Patients with invasive bilateral breast cancer were not included. Treatment: T (30 mg/m^2) iv day 1, 8 and 15, A (50 mg/m^2) iv day 1 and X (1500 mg/m^2 o.d.) days 1–14, in a 4 weeks course. This scheme was repeated up to 4 cycles followed by surgery. According to investigator criteria patients receive a maximum of six cycles. Radiotherapy and hormonal treatment are allowed depending on molecular markers. Expression of markers was performed by inmunohistochemistry before chemotherapy.
Results: thirty-four patients were included in this interim analysis, with a median age of 48 years (25–68). The ECOG PS was 0 in 31.3% and 1 in 68.8% of patients. Hormonal receptor status was ER+ 30%, PR+ 42% and C-erb2+ 50%. Primary tumour sites were breast: left (n = 18) and right (n = 16). A total of 118 cycles (median 3.5, range 1–4) were administered. Median relative dose intensity was 87% for T, 91% for A and 92% for X. Thirteen patients are still undergoing treatment; of 29 evaluable patients for efficacy, 9 achieved CR, 19 PR and 1 PD resulting in an ORR of 96.6% (95%CI: 90–100). Surgery was performed in 25 patients: three (12.0%) of them achieved pathological CR. All patients were evaluable for toxicity. Grade III/IV toxicity per patient was neutropenia (70.6%), leucopenia (50.0%), febrile neutropenia (8.8%); diarrhea (11.8%), mucositis (11.8%), nausea/vomiting (5.9%), dysgeusia (5.9%) and asthenia (2.9%). Median follow up time was 5.7 months.
Conclusions: T, A and X every 28 days administered during 4 cycles as neoadjuvant chemotherapy in locally advanced or inflammatory breast cancer is an active and well tolerated regimen.

478 PUBLICATION

Preliminary analysis of cisplatin (C) and gemcitabine (G) as second-third line treatment in metastasic breast cancer (MBC)

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Background: Combination C and G has demonstrated to be an active treatment in patients (p) with MBC. The less number of previous treatments for MBC more effectiveness this combination has shown. We conducted a study of C and G to evaluate the activity and toxicity profile of this combination.
Patients and methods: P with histological confirmation of MBC, ECOG performance status < 2, age > 18 years and adequate bone marrow, hepatic and renal functions, were included. Prior therapy with anthracyclines, taxanes and herceptin (erb-2 positive p) is mandatory. Treatment: C 25 mg/m^2 iv day 1, 8 and G 1000 mg/m^2 iv day 1, 8, every 3 weeks. At least 6 cycles was administered and the schedule was continued until progressive disease, unacceptable toxicity, consent withdrawal or investigator criteria. Response was evaluated every 3 cycles according to RECIST criteria.
Results: 31 p were enrolled, with a median age of 57 years (31–76), ECOG PS was 0–1 in 92.9% of p, hormonal receptor status was positive in 51.6% and ductal carcinoma in 93.1% of p. Median number of metastatic sites was 2 (83.9% with $\geqslant$ 2 sites), bone (58.1%), lung (41.9%), liver (38.7%) and nodes (38.7%), mainly. Neoadjuvant and adjuvant chemotherapy was administered to 23% and 77% of p respectively, 26% of p had received a second line treatment of chemotherapy for advanced disease and none received a third line. P received anthracyclines in a 97%, taxanes in a 90% and herceptin in a 29% (of erb-2 positive p). Up to date, a total of 130 cycles (median 3, range 1–10) were administered. Median relative dose intensity was 95% for C and 97% for G. Intent-to-treat efficacy analysis: over 21 evaluable p, 1 achieved CR, 6 PR, 5 SD and 9 PD, resulting in an ORR of 33.3% (95%CI: 13.1–53.5). Ten p were not evaluated: 1 protocol deviation, 1 lost of follow-up, 2 withdrawal consent and 6 ongoing with no evaluation yet. All p were evaluable for toxicity. During C-G treatment, grade III/IV hematologic toxicity shown per p was neutropenia (22.6%) and anaemia (9.7%). Grade III/IV non-hematologic toxicity shown per p was nausea (6.5%), vomiting (6.5%), asthenia (6.5%), anorexia (3.2%) and fever (3.2%). Median follow up time was 3.8 months, median time to progression was 7.5 months (95%CI: 0.8–14.2) and median overall survival 9.4 months (95%CI: 4.6–14.3).
Conclusion: In the interim analysis, G and C combination appears to be an active and well-tolerated regimen as second-third line in p with MBC.

479 PUBLICATION

Capecitabine second-line monotherapy for metastatic breast cancer

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Objective: objective measures of response and survival have been the targeted endpoints in clinical trial design and in physician selection of therapy for metastatic breast cancer (MBC). The evidence suggests that therapy for MBC should be continued until disease progression or development of unacceptable toxicities. Capecitabine is a useful and active oral chemotherapy in MBC, both in combination with paclitaxel in anthracycline-pretreated patients, and as moinotherapy in heavily pretreated patients. The proven activity of Capecitabine has provided the rationale to explore its use earlier in the course of the metastatic disease. Also there is a rationale for Capecitabine as maintenance therapy after response until progression.
Material and methods: The characteristics of the 62 evaluable patients(median age = 53 years) were well balanced. Around one half (46%) patients has more than one metastatic site involved. More than two-thirds (68%) of the patients has visceral metastases. All patients received first-line chemotherapy regimen. Approximately half of the patients had progressed while on prior anthracycline therapy; the others had progressed within 12 months of anthracycline therapy. Almost two-thirds(62%) of the patients had been exposed to 5-fluorouracyl (5-FU) and anthracyclines(67%).
Combination therapy consisted of Capecitabine 1250 mg/m^2 twice daily for 2 weeks of every 3-week cycle until grade 3/4 toxicities or progression.
Results: 62 patients are enrolled from our institution. Baseline characteristics were: median age 53 (34–75) years, KPS 80% (60–100%), 46% had 2 or more involved sites.
Median number of cycles was 9 (3–18). There were 17 complete and 32 partial responses so far (overall response rate in evaluable patients 69.5% [95%CI: 49.5–74.3%]) A further 19 patients had disease stabilisation.
The median time to disease progression was impressive. The primary objective of the study, to achieve a response rate in the range of 25–30% with Capecitabine, was met.
Furthermore, the time to disease progression and survival data (median survival in the subpopulation of patients who responded had not been reached at the time of the data analysis) were also encouraging. There were only five (5) relapses in this study so far. Hand–foot syndrome and gastrointestinal adverse events were the predominant toxicities. Most adverse events were mild: the incidence of grade 4 toxicities was very low, and the incidence of grade 3 hand–foot syndroma was <10%.