445 PUBLICATION

Fulvestrant in heavily pretreated patients with advanced breast cancer: experience from a Named Patient Programme in Switzerland

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Background: Fulvestrant (Faslodex®) is a new oestrogen receptor (ER) antagonist that downregulates the ER and has no agonist effects. Two randomised Phase III trials showed fulvestrant was at least as effective as anastrozole for time to progression, objective response and overall survival in postmenopausal women with advanced breast cancer (ABC) after progression/recurrence on tamoxifen. Here we report the efficacy and tolerability of fulvestrant when used in daily practice in a free of charge Named Patient Programme (supported by AstraZeneca) that was approved by the Swiss National Health Authority (Swissmedic). The majority of patients (98%) had received at least two prior endocrine therapies with or without chemotherapy.
Material and methods: Between December 2000 and May 2004, 179 postmenopausal patients with ABC were included. Therapy duration was measured from first supply of drug to withdrawal or last resupply date (where no withdrawal information was available). 28 patients were excluded from the efficacy analysis because of insufficient baseline/follow-up data; all were included in the safety analysis.
Results: Patients had a median age of 66 years (range: 27–91 years) and 93% had metastatic disease including 93 patients (62%) with bone metastases and 61 patients (40%) with visceral metastases (liver, lung). Most patients (87%) had received ⩾3 prior therapies for ABC (range: 1–10); 137 patients (91%) had received tamoxifen, 138 patients (91%) had received a non-steroidal aromatase inhibitor (AI) and 89 patients (59%) a steroidal AI. 40 patients (26%) were chemotherapy-naïve. 52 patients (34%) received fulvestrant for >6 months, 23 patients (15%) >1 year and six patients (4%) are still receiving treatment (current durations of treatment range up to 51+ months). Duration of therapy by site of metastases is shown in the table.

	Duration of therapy (months)				
Site of metastases (n)	⩽6	6–12	12–18	18–24	>24
No visceral metastases	39	16	3	4	2
Bone only	31	14	2	4	1
With visceral metastases	44	11	3	1	1
Visceral only	8	4	1	1	0

Six patients (3%) had serious adverse events (SAEs); two (1%) were suspected to be related to fulvestrant (facial flush with cough; deep vein thrombosis).
Conclusions: Fulvestrant showed good efficacy and tolerability in this heavily pretreated patient population. Notably several patients experienced prolonged disease stabilisation with fulvestrant, as seen in other studies. Fulvestrant offers a new convenient treatment option for postmenopausal women with ABC.

446 PUBLICATION

A Phase II trial of trastuzumab (H) plus capecitabine (X) as first-line treatment in patients (pts) with HER-2-positive metastatic breast cancer (MBC)

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Background: Breast cancer is one of the most common malignancies among Chinese women. The mortality rate has increased over the past 20 years: in the Zhejiang Province of China (urban area), the mortality increased from 6.56/100,000 in 1990–1992 to 8.01/100,000 in 2000–2002. The addition of H (Herceptin®) to a taxane in pts with HER2-positive MBC provides significant clinical benefit, including prolonged survival. H adds little to the toxicity profile of the taxane alone. As monotherapy, X (Xeloda®) has consistently high activity and a favourable safety profile. The addition of X to docetaxel extends survival in MBC. Preliminary data (Bangemann et al. 2000) indicated that the combination of H and X is an effective and well-tolerated therapy for intensively pretreated HER2-positive MBC (ORR 47%). The current study was initiated to evaluate the activity and safety of the combination of H plus X as first-line therapy in HER2-positive MBC.
Materials and methods: 48 pts were enrolled between March 2003 and October 2004. All pts had measurable (WHO criteria), HER2-positive (IHC 3+ or IHC 2+/FISH positive) MBC, KPS ⩾60, and adequate bone marrow, renal and hepatic functions. Pts had not received prior chemotherapy for MBC. H was administered as a 4 mg/kg loading dose followed by 2 mg/kg i.v. weekly (until disease progression) together with X = 1250 mg/m^2 twice daily on days 1–14 every 3 weeks (maximum 6 cycles).
Results: 43 pts received at least 9 weeks, 38 pts at least 18 weeks, 33 pts at least 26 weeks, 11 pts at least 34 weeks, and 3 pts at least 50 weeks of treatment. Baseline characteristics (n = 43): median age 49 years (range 27–74), median KPS 90 (range 60–100). The principal tumour sites were: lymph nodes (49%); lung (33%); liver (28%); breast (14%); thoracic wall (9%); chest (9%); other (5%). Prior treatment included: surgery (74%); radiotherapy (19%); and adjuvant chemotherapy (65%), including anthracycline (42%), docetaxel (9%), paclitaxel (7%) and other (19%). 43 pts are evaluable for safety. The most common grade 1/2 adverse events were: HFS (23%); leucopenia (9%); SGOT abnormality (9%) and SGPT abnormality (7%). Grade 3 HFS occurred in 4 pts (9%); grade 3 leucopenia occurred in 1 pt (2%). These grade 3 events improved/resolved in all pts. 43 pts are evaluable for efficacy. The ORR is 63% (n = 27), including 8 CR (19%) and 19 PR (44%). 13 pts (30%) have stable disease. Median progression-free and overall survival have not yet been reached.
Conclusions: These results confirm that the combination of H and X is a highly active and well-tolerated regimen for first-line treatment of HER-2-positive MBC.

447 PUBLICATION

Analysis of trastuzumab and chemotherapy in advanced breast cancer after the failure of at least one earlier combination: an observational study

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Introduction: In HER-2 overexpressing advanced breast cancer (ABC) the use of trastuzumab (T) in combination with chemotherapy to increase response rates and survival is well established. It is not known however, if treatment should continue after the failure of an earlier combination. We report our experience in patients with ABC who were treated with at least two lines of T containing regimens.
Patients and methods: We analysed retrospectively for time to tumour progression (TTP) for 1st, 2nd and beyond 2nd line treatment, response rates and overall survival (OS) using the Kaplan-Maier product limit method. Median time of observation was 24 months (m) (range 7–52 m).
Results: Thirty-five patients (pts), median age 50 years (y), range 25–73 y, were included into this study. The most common combination partners were vinorelbine (n = 38), capecitabine (23) and docetaxel (18). Response rates for 1st line treatment were 5.7% complete remission (CR), 40% partial remission (PR), 45.7% stable disease >6 months (SD) and 8.6% of patients experienced disease progression despite treatment (PD). Corresponding numbers for 2nd line were 5.7% CR, 28.6% PR, 37.1% SD and 28.6% PD. Numbers for treatment beyond 2nd line (42 therapies, 3rd to 7th line) were 28.6% PR, 31% SD and 40.5% PD respectively, translating into clinical benefit rate (CR+PR+SD>6 mo) of 91.4% for 1st line treatment, 71.4% for 2nd line and 59.6% for beyond 2nd line. Two pts showed response to a sixth line treatment. TTP was 7 m (range 1–17 m, 95%CI: 6.35–7.65) in the first line setting, 6 m (1–20 m, 95%CI: 4.54–7.46) in the second line and 6 m (1–41 m, 95%CI: 5.05.2–6.95) beyond second line. Log rank test revealed no significant difference. Median OS was not reached yet. Toxicities: A drop of left ventricular ejection fraction below 50% was observed in one patient, necessitating a discontinuation of T treatment. No case of symptomatic congestive heart failure was observed. All other toxicities were well within the range expected from the chemotherapy regimens.
Conclusion: The retrospective character of this study and the relatively low number of pts limit results. We are however able to strengthen existing evidence that pts profit from continuing T beyond 1st line. Further, this is among the first studies reporting a possible beneficial role of T containing

regimens even beyond 2nd line. Albeit these data, it is still necessary to include patients in randomised trials, to make a final conclusion possible.

448 PUBLICATION

Radiosensitized treatment of metastatical breast cancer with hemetoporphyrin derivative

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Background: Currently the methodologies that are used in oncology are quite of limited possibilities; therefore, there is a constant search for new, perspective treatment methods. One of such methods is sensitized tumor therapy based on quite selective porphyrin accumulation in tumors. Most widespread method of such treatment is photodynamic therapy (PDT). Applying PDT, a sensitizer is activated by visible light. Unfortunately, visible light can penetrate into a tissue only for several cm. This greatly narrows the indications of PDT. In 1987 we suggested new method, which remarkably broadens the possibilities of PDT application. We proved that some haematoporphyrin derivatives (HpD) can be activated by the ionizing radiation rays of certain power. During such radiosensitized tumors treatment (RST) the patient is injected with HpD and the tumor is irradiated with small amounts of gamma rays. The purpose of this report was to review our primary results of RST of metastatical breast cancer.
Materials and methods: Since 2001 the 11 patients with advanced breast cancer underwent RST. HpD was injected i.v. with a dose of 5 mg/kg body weight. 24, 48 and 72 h after injection of the sensitizer tumors were irradiated with gamma rays – 2 Gy at a time from radioactive cobalt. The full dose of a course was 6 Gy. 3 patients underwent one course of the treatment, for the rest 8 the treatment was repeated after 1–4 mo. The bone metastases of bone were estimated in 8 patients. The metastatical lung lesions – in 3 patients. The multiplex brain metastases were diagnosed in 4 patients, lymph node metastases – in 5, hepatic metastases – in 4 patients. In one patient multiplex metastatical lesions of soft tissue were identified and in one – the conjunctival metastasis was finded. In all these cases patients underwent RST as palliation.
Results: As the immediate result of RST of advanced breast cancer approximately 15% of all metastatical lesions fully disappeared after single course of RST. The best effect was noticed in bone and brain metastases. The effectiveness of RST of lymph nodes and hepatic metastases was slight. The significant response was observed in 6 patients. Only for one patient the treatment was ineffective.
Conclusions: RST is effective method in metastatatical breast cancer. The effectiveness of RST depends on the location of metastases.

449 PUBLICATION

Navelbine-Doxorubicin combination chemotherapy is an active and safe regimen for patients (pts) with Advanced Breast Cancer (ABC): Final results of a large Syrian. Phase II trial

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Background: Navelbine (N) and doxorubicin (A) are active agents in the management of breast cancer. Several international studies reported the definite efficacy of N+A in advanced or in early disease (Blagman; cancer 99, Smith; ASCO 03).here we report our experience of a large Phase II trial conducted in our cancer center with N-A combination in ABC.
Patients and methods: Eligible patients had confirmed locally advanced(LABC)(tumor size > 3 cm of diameter) or chemonaive metastatic breast cancer(MBC) WHO PS$\leqslant$ 2, measurable disease, no prior therapy, Adequate bone marrow, renal and liver functions. Patients received N: 25 mg/m^2 on day 1 and day 8, plus A: 50 mg/m^2 on day 1. Cycles were repeated every 3 weeks. Patients with LABC were restaged after 3 cycles; pts showing clinical CR or PR received 3 additional cycles of the combination. Patients with MBC were evaluated every 2 cycles for response and every cycle for toxicity.
Results: Sixty-six patients were enrolled into the study, 36 pts with LABC, and 30 with MBC at presentation. median age was 46 years (range 25–67), WHO PS 0–1, median tumor size 6 cm (2–16). 50% of pts with MBC had visceral involvement. All pts were evaluable for efficacy and safety. Thirty-one pts with LABC achieved clinical objective responses (ORR = 88%) including 55% of clinical complete response. 68% of pts received Breast conservative surgery was performed in 68% of pts and pathological complete responses observed in 35% of pts. Twenty-four pts with MBC achieved objective responses (ORR = 80%) including 30% of CR. This combination was well tolerated, a total of 298 cycles were administered with a median number of 5 cycles by pts (1–6) WHO grade 3–4 neutropenia occurred in 25% of pts. and G3 anemia in 2 pts Non-hematological toxicity was mild and manageable, alopecia was universal, there were no severe nausea/vomiting, neuropathy or constipation.
Conclusion: Results of our study are similar to the international data and confirm that NA is highly active and safe regimen for BC pts.

450 PUBLICATION

Evaluation of fulvestrant (F) activity and toxicity in heavily pretreated patients with advanced breast cancer (ABC)

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Background: F is an estrogen receptor antagonist with no agonist effect. Although F showed a similar activity to anastrozole when given as first/second line to patients with ABC resistant to tamoxifen, its activity in heavily pretreated women is not well documented.
Methods: Forty-six postmenopausal (16/46 induced by LH-RH analogue) women received F 250 mg i.m. q 28 days (Faslodex® compassionate use program by Astra-Zenaca, Italy), after the failure of previous endocrine treatments (median: 4, range 1–7 lines). Thirty-nine patients also received previous chemotherapy (median 5, range 1–12 regimens) for advanced disease. Namely, 30 pts received F as 4th–7th endocrine treatment and 33 pts after 4 to 12 chemotherapy regimens. Patients were treated until disease progression/unacceptable toxicity/treatment refusal.
Results: Fulvestrant toxicity and activity were registered every 4 and 12 weeks, respectively; 42 pts were evaluable for response. The median length of treatment administration was 4 months (2–15+). Fulvestrant was very well tolerated, with no G2–4 NCI-CTC toxicity. Overall, no CR/PR were observed. Nineteen pts (45%) had SD and 23 pts (55%) progressed. Twenty-four out of 42 pts received F at the time of tumour progression, 20/24 being valuable for response (4 pts: too early): 8/20 obtained a SD (3 pts: > 3 months < 6; 5 pts: $\geqslant$ 6 months). All these 8 pts were pretreated with both endocrine treatment (median: 3, range: 2–5 lines) and chemotherapy (median: 5, range 1–11 regimens) for advanced disease.
Conclusions: F is well tolerated and can obtain a sustained disease stabilization in heavily pretreated ABC with tumour progression at the time of treatment starting.

451 PUBLICATION

Morphological type as prognosis factor for conservative surgery of locally advanced breast cancer

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Background: To research morphological type as prognosis factor for conservative treatment in group patients with locally advanced breast cancer (T2–3N0–1M0); (T0–3N1–2M0).
Materials and methods: Four hundred and forty seven women 447 with locally advanced breast cancer were treated from 1986 to 2001 at the Russian Cancer Research Center. Two hundred and twenty seven 227 women underwent quadrantectomy with axillary dissection and radiotherapy. Two hundred and twenty 220 women underwent different variants of radical mastectomy (Patey or Madden). Women from both groups received neoadjuvant and adjuvant therapy. 320 (71.6%) was diagnosed invasive ductale cancer, invasive lobular cancer was in 72 (16.1%), combination invasive ductale and lobular cancer was in 21 (4.7%). The medicine follow-up was 54 months.
Results: 5 years overall survival in patients with invasive ductale cancer in group of mastectomy was 81.0$\pm$3.9%, in group of quadrantectomy – 85.2$\pm$8.3% in patients with invasive lobular cancer – 82.4$\pm$8.3% and 81.5$\pm$6.5% ($p > 0.05$). 5 years desease-free survival was poor in group of quadrantectomy in patients with invasive lobular cancer – 63.0$\pm$6.5% compare with group of invasive ductale cancer – 74.5$\pm$3.0% ($p < 0.05$). In group of radical mastectomy in patients with invasive lobular cancer – 73.6$\pm$8.0% and invasive ductale cancer – 76.6$\pm$4.9% ($p > 0.05$).
Conclusion: 5 years desease-free survival was poor in group of quadrantectomy with invasive lobular cancer compare invasive ductale cancer. Invasive lobular cancer is factor of risk locally recurrences conservative surgery in patients with breast cancer.