Proffered Papers

Breast cancer advanced disease

1255 ORAL

The added value of the combined evaluation of clinical efficacy, quality of life and cost-effectiveness in a randomized phase III study. Results of an EORTC – NCIC – SAKK neoadjuvant trial in patients with locally advanced breast cancer (LABC)

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Background: Between 05/93 and 04/96, 448 patients (pts) with LABC were randomized into a study comparing: F (500 mg/m^2 i.v. d 1, 8), E (60 mg/m^2 i.v. d1, 8) and C (75 mg/m^2 p.o. d 1–14) q 28 d ' 6 (arm A) Vs E (120 mg/m^2 i.v. d1), C (830 mg/m^2 i.v. d 1) and G-CSF (5 μg/kg/d s.c. d 2–13) q 14 d ' 6 (arm B). The main endpoint was progression free survival (PFS). Other endpoints included overall survival (OS), toxicity, quality of life (QoL) and cost-effectiveness (CE).

Methods: The clinical efficacy based on a potential difference in progression free survival was evaluated on all eligible pts included in the study. The QoL was assessed using the EORTC QLQ-C30 for all pts included in the European component of the study. The CE evaluation was conducted for pts recruited by French, Belgian, Dutch and British centers. The CE evaluation was based on both a specific questionnaire completed by the patients and cost data collected at each institution.

Results: Although the dose intensity delivered in arm B was twice as high as in arm A, there is no significant difference in PFS and OS between the two arms after a median follow-up of 3 years. Compared to arm A, arm B had a significantly poorer Qol score during the first 3 months. However, Qol returned to that of baseline levels earlier for this group of patients and over the first year there was no significant difference in Qol between the two groups. CE analysis disclosed differences in resource use between treatment arms and also between countries and between centers from the same country.

Conclusion: Although arm B provides the same efficacy as arm A with a shorter duration of treatment, its further implementation into day-to-day practice may be hampered by the available Qol and CE data. These exploratory analyses have revealed important aspects of the treatments under investigation that could not have been appreciated solely on the basis of the clinical data.

1256 ORAL

Comparison of outcomes in high risk, locally advanced and inflammatory breast cancer treated with high dose chemotherapy (Quartet) versus standard doxorubicin-based regimens

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From Jan 92 to Dec 95, 87 patients entered a Phase I/II trial of 15 weeks of doxorubicin dose-intense chemotherapy (with cyclo, MTX, Cisplatin, 5 FU, VP 16) followed by 3 days of high dose cyclophosphamide (C), etoposide (V) and cisplatin (P) at week 17 plus GMCSF (Hoescht) or G-CSF (Amgen). CVP total dose (wk 17) between C 4.2–4.8 g/m^2, V 1.5–1.8 g/m^2, P 75 m g/m^2 then RT and TAMxSy. All <56 y, no metastatic disease and either 8 or more +ve nodes (32) or clinically or pathologically locally advanced (T3, 4 or N2) (45) or inflammatory (T4D, any N) (10) breast ca. Failure-free (FFS) and overall survival (OS) were compared with Quartet and 2 matched groups (1) historical group of all similar patients (142) referred to BCCA between Jan 1989 and Dec 1991 who had received a standard dose doxorubicin-based regimen (CAF, AC or ACMF) (2) all similar patients (166) between Jan 92 and Dec 95, concurrent with Quartet study, who were not enrolled and (3) the combination of all pts in groups 1 & 2.

Results: At med-follow-up 4.2 y, overall and failure free for Quartet are 63% and 52%. Comparisons with historical control groups show NO difference for all pts or subsets.

1257 ORAL

Preliminary results of a large comparative multi-centre clinical trial comparing the efficacy and tolerability of Armidex™ (Anastrozole) and Tamoxifen (TAM) in postmenopausal women with advanced breast cancer (ABC)

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Purpose: 'Arimidex' (anastrozole) (AN), a non-steroidal aromatase inhibitor, is available for treatment of ABC in postmenopausal women recurring/progressing on TAM treatment. Here we present the results of a trial comparing the efficacy and tolerability of AN with TAM in postmenopausal women with ABC.

Methods: This randomised, double-blind trial was designed to demonstrate equivalent efficacy of AN 1 mg once-daily relative to TAM 20 mg once-daily in ER+ve and/or PR+ve or unknown patients eligible for hormonal therapy (HT). Patients may have received prior adjuvant HT or chemotherapy; a drug-free period of Ú 12 months was required for those patients who received adjuvant TAM. The primary endpoints of the trial were time to progression (TTP), objective response (OR), and tolerability.

Results: 668 patients were randomised on a 1:1 basis and followed for a median of 19 months. Disease progression was observed in 73% of AN and 75% of TAM patients. Median TTP was 8 months for both groups. OR (CR + PR) was 32% for both AN and TAM. Clinical benefit rates (CR + PR + SDU 24 weeks) were 56% for AN and 55% for TAM.

	Est Value	Lower 95% Conf Limit	Equiv Criterion
Haz Ratio (TTP) TAM/AN	0.99	0.85	0.80
Diff in OR (AN – TAM)	–1%	–7%	–10%

The % incidence of selected pre-defined side effects were as follows for AN and TAM respectively: Hot flushes (21% and 21%), thromboembolic events (5% and 7%), GIT disturbances (23% and 28%) and lethargy (1% and 3%).

Conclusion: 'Arimidex' satisfied the pre-defined criteria for equivalent efficacy to TAM, with a lower observed incidence of thromboembolic events, and may be considered as an alternative first-line treatment to TAM in postmenopausal women with ABC.

1258 ORAL

Side effects of endocrine therapy in patients with breast cancer

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Six hundred women on endocrine therapy were assessed using the C-PET questionnaire [Ray, Brit Med J 1996 313 1484] for symptoms associated with standard hormonal interventions. Tamoxifen caused similar symptoms whether used for advanced disease or in the adjuvant setting and patients were therefore regarded as one group. The groups compared were tamoxifen, T, [505 patients] anastrozole, A, [77 patients] and megestrol, M, [16 patients]. Incidence of side effects was scored as absent or present. The following side effects were reported, hot flushes [H] 54%, sweats [S] 53%, weight gain [W] 39%, fluid retention [F] 21%, nausea [N] 10%, impaired libido [L] 17%, irritability [I] 12%, low energy [E] 26%, dyspnoea [D] 16% and vaginal bleeding [VB] 7% or dryness [VR] 21%.

Multiple 2 × 2 chi-square comparisons, thus $p < 0.01$ significant.

%	H	S	W	VB	VR	D	N	E	I
T	57	56	41	8	29	16	8	25	10
A	39	38	23	1	22	14	22	36	22
M	37	43	56	19	12	50	1	44	18

A versus T showed significantly lower incidence of H, S, W, VB and VR [range of $p < 0.005$] and higher incidence of N and I for A[$p < 0.01$]. D was significantly higher for patients on M as compared to both T and A[$p = 0.002$]. Side effects are frequent and may be clinically distressing on any of the three drugs. Against the new aromatase inhibitors the problem of megace tolerance is well recognised but the tamoxifen comparative toxicity is of interest in view of the current adjuvant trials.

1259 ORAL

A phase II randomized study of doxorubicin (A) alternated to docetaxel (T) (ALT) vs sequential administration of 4 cy of t followed by 4 cy of a (seq) as 1st line ct in mbc pts

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From 3/96 to 3/98, 106 pts with untreated MBC were treated with T (100 mg/m^2) and A (75 mg/m^2) on an Alt cy by cy (A.T.A.T.A.T.A.T) or Seq (T.T.T.T.A.A.A.A) basis q3w for a maximun of 8 cy.

Eligibility: meas MBC, age < 75 y, WHO PS 0–2, no prior CT for MBC (prior adj. allowed provided <240 mg/m^2 of prior A) and adequate hemato, renal, hepatic and baseline LVEF. Pts characteristics were well balanced: med age 55 y (29–75), med PS 1 (0–2). Adj. CT: 88% of pts (with anthracycline in 3 pts). Tm charac: Alt/Seq (% pts): visc (82/80), liver (47/54), bone (39/51) and >2 organs (43/40).

Results: med nb of cy is 8 in both arms. Febrile neutropenia and gr 3 inf was observed in 18% Alt and 13% Seq of pts. Except stomatitis (more frequent and more severe with Alt), no other non-hematological severe or gr 3/4 adverse events were observed. With a med. F-up of 14 mo and a med. cum dose of A of 300 mg/m^2, no CHF was observed. Fluid retention was severe in only 1 pt. Activity was similar between Alt/Seq: ORR% 60/67, CR% 2/7, Liver RR% 59/62, Resp Dur wks 47/44, TTP wks 39/38 respectively. As of 3/99 med survival was not yet reached in both arms.

Conclusion: Alt and Seq administration of A and T are safe, feasible and effective regimens. A comparison of Alt or Seq administration of A and T with AT combination is warranted.

1260 ORAL

Randomized open-label phase III multicenter trial comparing TAXOL®/doxorubicin (AT) versus 5-fluorouracil/doxorubicin and cyclophosphamide (FAC) as a first line treatment for patients with metastatic breast cancer

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Objectives: To compare time to progression, response rate, survival safety and quality of life.

Patients: Histologically proven breast carcinoma, previously untreated with chemotherapy for metastatic disease, no prior anthracyclines and/or taxanes, one prior adjuvant chemotherapy allowed if >6 months.

Treatment: Patients received AT: A = 50 mg/m^2 and TAXOL (3-hour infusion at 220 mg/m^2 given 24 hours after doxorubicin) or FAC: F = 500 mg/m^2, A = 50 mg/m^2 and C = 500 mg/m^2 every 3 weeks, for 8 courses. Standard 3-drug premedication was given prior to TAXOL.

Results: From 25Nov96 to 30Mar98, 267 patients were randomized in 29 centers (Central and Eastern Europe, Israel). This randomization was stratified for center, prior adjuvant chemotherapy (AT: 43% – FAC: 44%) and presence of bone metastases (AT: 36% – FAC: 35%). 131 patients were treated with AT and 133 with FAC. The median time to progression (TTP) was significantly superior ($p = 0.034$) for AT: 8.3 months than for FAC: 6.2 months. The overall clinical response rate was 68% in the AT and 55% in the FAC arm ($p = 0.032$) (CR: 19% vs. 8%). Main grade 3–4 toxicities by patient showed: AT is more toxic in terms of neutropenia (89% vs. 65%) but not in terms of febrile neutropenia (8% vs. 5%). Grade 3–4 arthralgia/myalgia (10% vs. 0%), PNS (12% vs. 0%) and diarrhea (2% vs. 0%) was more frequently observed in AT arm. More Grade 3–4 nausea/vomiting (8% vs. 18%) in FAC arm. AT showed delayed CHF in <2% of patients; 1 CHF was observed on-study in FAC.

Conclusion: AT showed a significant advantage in TTP compared to FAC. Preliminary survival data are confirming the efficacy advantage with AT combination but more follow-up is needed.

1261 ORAL

Herceptin (R) improves time to progression following chemotherapy in women with metastatic breast cancer

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Purpose: To assess the efficacy of Herceptin (trastuzumab) in combination with chemotherapy as first-line treatment for women with metastatic breast cancer overexpressing HER2.

Methods: Women were allocated to either doxorubicin/epirubicin plus cyclophosphamide (AC) alone or AC + Herceptin (H) if they had not received previous adjuvant AC. Women who had received previous AC were allocated to paclitaxel (T) or T + H. Doses: Doxorubicin = 60 mg/m^2, epirubicin = 75 mg/m^2, C = 600 mg/m^2, T = 175 mg/m^2 every 3 hours; all chemotherapy was given every 3 weeks for 6 cycles. H = iv 4 mg/kg loading dose then 2 mg/kg every week.

Results: Responses to treatment were confirmed by an independent Response Evaluation Committee. Assessments of response rates and time-to-disease progression (TTP) showed a significant improvement of chemotherapy effect in patients receiving H.

N	RR (%)	TTP (months)	
Chemo	234	32	4.6
Chemo + H	235	49 p = 0.0002	7.6 p = 0.0001
AC	138	43	6.1
AC + H	143	52 p = 0.1038	8.1 p = 0.0003
T	96	16	3.0
T + H	92	42 p < 0.0001	6.9 p = 0.0001

Conclusions: Addition of Herceptin to chemotherapy increased response rate and time-to-disease progression significantly compared with chemotherapy alone.

1262 ORAL

The palliative effect of chemotherapy (CT) in metastatic breast cancer (MBC): Objective tumour response is associated with symptom (Sx) improvement

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Purpose: Providing palliation is a major goal of CT in MBC. However, most trials report response rates and not Sx palliation. This study investigated the association between objective response and improvement in cancer Sx.

Methods: 300 MBC patients (pts) who participated in an NCIC CTG trial of doxorubicin +/− vinorelbine were studied. The 9 most common Sx present at baseline on the EORTC Quality of Life Questionnaire (QLQ-C30) (QoL) and on the toxicity section of case report form (CRF) were selected. Sx improvement, stability and worsening were defined and assessed during therapy using serial QoL and CRF data. The relationship between Sx change and response (CR, PR, SD and PD) was examined using 3 × 3 tables of categorical data and a linear trend test (logistic regression model).

Results: Three baseline Sx (pain, shortness of breath and abnormal mood) showed a significant relationship ($p < 0.05$) between likelihood of improvement and objective response using CRF and QoL data. Constipation, anorexia and nausea showed similar results only in the QoL data. The converse was seen for lethargy. The remaining Sx: cough and insomnia, did not show a trend.

Conclusion: Certain cancer Sx improved in concert with CT related tumor shrinkage in this study. Further work in this area will be useful to determine the surrogate value of objective response in relation to the palliative effect of CT.