Proffered papers

Breast cancer — adjuvant therapy

44 ORAL

RADIOTHERAPY IN LOCALLY ADVANCED BREAST CANCER

M. Adelina Costa, H. Gomes Pereira, M. José Bento, Élio Vieira
Department of Radiotherapy-Instituto Português de Oncologia Porto, Portugal

A review of 300 cases of locally advanced breast cancer, referred to the Instituto Português de Oncologia, Porto were studied from January, 1985 to December, 1988, to evaluate the therapeutic approach of Radiotherapy.

They were classified in two groups; the first one received Radiotherapy (52%) and the other one (48%) didn't.

Total survival and disease free survival curves were evaluated in relation to different parameters (hormonal state, histologic tumor grade, pathologic state, lymphnodes envolvement, local recurrence and distant metastasis). Survival rates were calculated according to Kaplan-Meyer's method and the differences between pairs of survival curves were assessed by the Logrank method. The significance level was $P < 0.05$.

A statistically significant improvement was observed in the group receiving Radiotherapy for most of the parameters ($P < 0.00001$), showing the importance of this treatment in the approach of locally advanced breast cancer.

45 ORAL

ERBB2 OVEREXPRESSION AFFECTS TAMOXIFEN EFFICACY IN THE ADJUVANT TREATMENT OF NODE NEGATIVE OPERABLE BREAST CANCER PATIENTS

C. Carlomagno[1,3], F. Perrone[1,3], R. Lauria[1,3], M. DeLaurentiis[1,3], C. Gallo[3], A. Morabito[1,3], G. Pettinato[2], L. Panico[2], S. DePlacido[1,3], A.R. Bianco[1]
[1]*Dipartimento di Endocrinologia ed Oncologia Molecolare e Clinica*
[2]*Istituto di Patologia, Università di Napoli "Federico II"*
[3]*Centro Elaborazione Dati Clinici in Oncologia del Mezzogiorno, CNR-ACRO*

Aim. To study retrospectively the interaction between ErbB2 overexpression and adjuvant tamoxifen in node negative breast cancer patients (pts) entered into the controlled clinical trial GUN-1 (*Lancet* 1988, ii: 1095). *Patients and Methods.* ErbB2 was evaluated by immunohistochemistry in 150 out of 173 pts who had been randomly assigned to 2-year adjuvant tamoxifen (TM) (n. = 90) or no further therapy (n. = 60). ErbB2 was defined positive if more than 10% of cells showed specific membrane staining. *Results.* As of November 30, 1994, median follow up is 12 years. ErbB2 was overexpressed in 44/150 pts (29.3%). The addition of ErbB2 to a multivariate Cox model, containing age, menopausal status, tumor size, nuclear grade and treatment as covariates, was not statistically significant, while the addition of first order interaction between ErbB2 and TM was statistically significant both for DFS and OAS; the same result was obtained also when the basal model contained estrogen receptor (ER) and ER-TM interaction. Indeed, adjuvant tamoxifen significantly prolonged DFS ($P = 0.0009$) and OAS ($P = 0.03$) only among ErbB2 negative cases, while no difference was observed in ErbB2 positive cases both for DFS ($P = 0.22$) and for OAS ($P = 0.12$).

Dr. De Laurentiis is recipient of an AIRC fellowship.

46 ORAL

UNEXPECTED OPPOSITE AGE RELATED EFFECT OF ADJUVANT HIGH-DOSE PROGESTERONE ACETATE (HD-MPA) FOR NODE POSITIVE (NP) EARLY BREAST CANCER: 10 YEARS RESULTS OF A MULTICENTER RANDOMIZED TRIAL

C. Focan, M. Beauduin, E. Salamon, J. de Grève, G. de Wasch, J.P. Lobelle, F. Majois, A. Tagnon, J. Tytgat, S. Van Belle, R. Vandervellen, A. Vindevoghel
Adjuvant Breast Cancer Project, Belgium

281 NP early breast cancer patients among whom 270 were fully evaluable were randomized to receive either no hormonotherapy (group A) or an hormonotherapy with HD-MPA (500 mg IM daily for 4 weeks then 500 mg IM twice weekly for 5 months); all patients received also 6 monthly courses of IV CMF.

Patients characteristics were well balanced among both groups. The toxicity of chemotherapy was evaluated on 2960 courses. In HD-MPA arm irrespectively of age, patients could better tolerate CMF chemotherapy with less WBC, granulocyte, nausea-vomiting toxicities and infections, and higher dose-intensities (P 0.02–0.0001) as well as higher dose intensity products (P 0.001–0.0001). Relapse free survival (RFS) and overall survival (OS) were not different at the whole group level (at 10 years: 0.50 in both arms) or as regard T, number of positive nodes, receptor categories, type of surgery or radiotherapy. However a striking difference was observed when patients were split according to age (<50; $\geqslant$ 50) or menopausal status. If older patients benefited from the combined treatment (at 10 years RFS: A: 0.38; B: 0.54 - P 0.003; OS: A: 0.52; B: 0.63 - P 0.11), younger patients had a significantly worse prognosis when treated with CMF + HD-MPA, (at 10 years: RFS: A: 0.67; B: 0.45 - $P < 0.01$; OS: A: 0.80; B: 0.53 - $P < 0.009$).

In conclusion: in less than 50 years patients, HD-MPA had a negative adjuvant impact both on RFS and OS. These results contrast with the results obtained in older subjects and with the excellent adjuvant impact of HD-MPA observed in node negative early breast cancer patients. This observation warrants further randomized evaluation in <50 years NP subjects comparing chemotherapy alone versus sequential chemo-hormonotherapy.

47 ORAL

SURGICAL COMPLICATIONS RELATED TO PERIOPERATIVE ADJUVANT CHEMOTHERAPY IN BREAST CANCER. RESULTS OF A PROSPECTIVE, CONTROLLED, RANDOMIZED CLINICAL TRIAL

G. Canavese, A. Catturich, C. Vecchio, M. Gipponi, D. Tomei, M.R. Sertoli, L. Repetto, F. Badellino
IST, V.le Benedetto XV, 10, 16132 Genoa, Italy

From May 1985 to June 1992, 375 patients (pts) were enrolled in a prospective controlled randomized clinical trial of periop adjuvant chemotherapy (PAC) associated to long-term adjuvant chemo-endocrinotherapy in order to test the effectiveness of reducing the time interval between surgery and chemotherapy. Here, the short-term surgical complications related to PAC are reported in order to verify whether such treatment might negatively affect the results of breast cancer surgery. Pts undergoing PAC received within 48–72 hour following surgery one course of CY (600 mg/sqm), EPI (60 mg/sqm), and 5-FU (600 mg/sqm) (CEF): pN+ pts, who were given perioperative CEF, had five further cycles of CEF alternated with six cycles of CMF (CY 600 mg/sqm, MTX 40 mg/sqm, 5-FU 600 mg/sqm). All other pN+ pts had six cycles of CEF alternated with six cycles of CMF, starting within 30 days after surgery. No significant difference of postop morbidity was observed in the two groups as regards median hospital stay (8 days), number of outpatient dressings (3.5 vs 3), seroma (51 = 26.9% vs 45 = 24.2%), lymphatic drainage (400 vs 409 ml), and postop infections,

both local (10 vs 9) and in extraop foci (6 vs 7). The toxicity of the periop CEF was mainly gastrointestinal (nausea and vomiting 55%, stomatitis 3%), with only a small percentage (9%) reaching grade III–IV.

48 ORAL

INFLUENCE OF CONCOMITANT RADIOTHERAPY ON DOSE INTENSITY OF ADJUVANT CMF IN PATIENTS WITH NODE-POSITIVE BREAST CANCER

R.J. Paridaens, J. Lemmens, N. Devadder, E. Van Limbergen, W. Van den Bogaert, J. Thomas, J. Wildiers[1], M.R. Christiaens[2]
[1]*Department of Oncology*
[2]*Department of Surgery, Univ. Hosp. Gasthuisberg, 3000 Leuven, Belgium*

We analyzed the impact of radiotherapy (RT) on dose-intensity (D/I) and complications of adjuvant postoperative CMF (6 cycles q 4W; CPA 100 mg/m^2 p.o. d1–14; MTX 40 mg/m^2 and 5-FU 600 mg/m^2 i.v. d1,8) in 100 node-positive breast cancer patients (pts). Doses were adjusted according to leucocyte counts. In 51 pts receiving chemotherapy only (CT), average D/I remained close to 100% during cycles 1 & 2, and decreased to 85% for cycles 3 to 6. In 49 pts receiving concomitant radiochemotherapy (RTCT), a significant loss in D/I occurred already during cycle 1, decreasing steadily below 80% during the last 2 cycles. Protracted leucopenia affected significantly D/I in pts having started RT more than 7 days before initiating CT. Premature treatment interruption, and complications (infections, anemia) were more frequent in RTCT than in CT pts. Thus, RTCT pts (mainly breast conserving surgery) are at high risk of receiving inadequate adjuvant CT. Hemopoietic growth factors may help to optimize the delivery of combined RTCT (ongoing study).

49 ORAL

ADJUVANT HIGH DOSE CHEMOTHERAPY (H.D. CT) WITHOUT BONE MARROW RESCUE IN BREAST CANCER PATIENTS (B.C. PTS) WITH 10 OR MORE POSITIVE AXILLARY NODES (N $\geqslant$ 10): PRELIMINARY FINDINGS FROM A GROCTA PILOT STUDY

F. Brema, F. Patrone, D. Amoroso, A. Ballestrero, C. De Sanctis, F. Ferrando, U. Folco, L. Irtelli, S. Mammoliti, M. Mesiti, P. Pacini, M. Rinaldini, M. Venturini, F. Boccardo, GROCTA Group
Headquarters: Department of Medical Oncology 2, Ist. Naz. per la Ricerca sul Cancro, Genova, Italy

40 N $\geqslant$ 10 b.c. pts (median age: 46 yrs, range 31–56; median number of involved nodes: 13, range 10–33) were entered so far into a pilot trial to evaluate the feasibility of an adjuvant H.D. CT program without the use of stem cell support. Pts were given 3 cycles of CYC 600 mg/m^2 d. 1, EPIDOX 60 mg/m^2 d. 1, 5-FU 600 mg/m^2 d. 1, q. 3 wks, followed by H.D. CT, administered in protect environment as needed, with CYC 2500 mg/m^2 dd. 1,2; VP16 500 mg/m^2 dd. 1–3; CDDP 50 mg/m^2 dd. 1–3. Granulocyte-colony stimulating factor (G-CSF) was administered in all patients beginning on day 5 from H.D. CT and continued until leukocyte count reached 10 $\times$ 10^9/L. Median duration of granulocytopenia <500/μl was 7 days (5–10) and that of thrombocytopenia <20.000/μl was 3 days (1–5). The recovery to an ANC of at least 500/μl took a median of 15 days (13–17). No toxic death occurred. Median red cell transfusion requirement was 2 unit (0–4), and median platelet unit requirement was 1 unit (1–4). At a median follow up time of 14 mos (range 1–27), 5 pts are relapsed and 2 are dead. In conclusion, H.D. CT for high risk b.c. pts seems to be feasible and promising even without bone marrow rescue. Supported in part by ACRO, CNR contract No 94.01242.PF39.

50 ORAL

RISK OF SECOND MALIGNANCIES FOLLOWING ADJUVANT CHEMO (CT) A/O TAMOXIFEN (T) THERAPY

F. Boccardo, A. Rubagotti, A. Perrotta, C. Casella, D. Amoroso
Italian Breast Cancer Adjuvant Study Group (GROCTA) and National Institute for Cancer Research, 16132 Genoa, Italy

Out of 1286 breast cancer patients (pts) receiving adjuvant therapy between 1983 and 1990: 656 were treated with T (10 mg TID) for up to 5 yrs, median age: 59, median F.U. time: 40 mos (30–134); 410 were treated with different CMF-based CTs, median age: 49, median F.U. time: 68 mos (30–135); 220 were given adjuvant CTT, median age: 55, median F.U. time: 91 mos (30–135). Four hundred and ten additional pts served as no treatment (NT) group. Median age: 60; median F.U. time: 83 mos (30–137). Overall 53 2nd cancers were documented in 1696 pts, 19 of which were contralateral breast cancers. Standardized Incidence rates (SIRs) were calculated using as reference the Lombardy Cancer Registry for the years 1983–87. The rate ratio of cancer in the NT group was calculated relative to each treatment group by determination of the ratio of the SIRs. Results are summarized below.

	NT	T	CT	CTT
SIRs	RR (95%C.I.)	RR (95%C.I.)	RR (95%C.I.)	RR (95%C.I.)
Total	0.8 (0.5–1.3)	0.5 (0.2–0.9)	1.9 (1.2–2.9)	0.7 (0.3–1.5)
Excluding b. ca.	0.7 (0.4–1.5)	0.4 (0.1–0.9)	2.0 (1.1–3.4)	0.7 (0.2–1.8)
Rate Ratios	-(-)	0.6 (0.3–1.9)	2.4 (1.4–4.5)	0.9 (0.3–2.5)

Actuarial cumulative hazard rates (%) at 5 and 10 yrs were: NT, 3/6.4; T, 1.75/3.1; CT, 4.5/17.5; CTT, 2.8/4.6: $P = 0.05$; CT vs CTT: $P = 0.08$; CT vs T: $P = 0.008$. *Conclusions:* pts treated with CT have a significantly increased risk of 2nd malignancies than those treated with T and than those in the NT group or general population. Pts treated with CTT seem to bear an intermediate risk.

51 ORAL

CLODRONATE IMPROVES BONE MINERAL DENSITY IN EARLY BREAST CANCER PATIENTS. A RANDOMIZED STUDY

T. Saarto, C. Blomqvist, M. Välimäki, P. Mäkelä, I. Elomaa
Department of Oncology, Helsinki University, Finland

The aim of the study was to investigate whether clodronate will improve bone mineral density (BMD) in pre- and postmenopausal patients without skeletal metastases.

Patients and Methods: 268 pre- (PRE) and postmenopausal (POST) early breast cancer patients were randomized to clodronate (orally 1.6 g a day) or control groups for 3 years. PRE were treated with adjuvant chemotherapy and POST with antiestrogen for 3 years. BMD was measured on the lumbar vertebrae L1–4 and the femoral neck before treatment and after two years.

Results: POST: Lumbar bone mass decreased 0.4% in control group and increased 0.9% in clodronate group ($P = 0.008$), in femoral neck the increase of bone mass was 0.3% in control group and 1.4% in clodronate group ($P = 0.04$). PRE: Lumbar bone mass decreased in both groups 2.7% in control group and 0.8% in clodronate group ($P = 0.008$). Femoral neck bone mass decreased 0.9% in control group and increased 0.4% in clodronate group ($P = 0.03$).

Conclusion: Clodronate significantly prevents bone loss in lumbar vertebrae and femoral neck in PRE and POST early breast cancer patients. In POST clodronate with antiestrogen significantly improves BMD in lumbar vertebrae and femoral neck. In PRE the bone loss was most markedly prevented in those who developed rapid bone loss after chemotherapy.

52 POSTER

RATES OF LOCAL RECURRENCE WITH NEOADJUVANT CHEMOENDOCRINE THERAPY FOR PRIMARY BREAST CANCER

J.R. Benson, T.J. Powles, A. Makris, G. Knee, S. Ashley, A.G. Nash
Breast Unit, The Royal Marsden Hospital, London and Surrey, U.K.

Breast conservation surgery for early breast cancer is associated with equivalent survival, but higher rates of local relapse than mastectomy. Pathological margin status and EIC are major determinants of relapse risk. In a randomised trial of chemoendocrine therapy administered either prior to or following primary surgery and radiotherapy, we have assessed neoadjuvant and adjuvant regimens on rates of loco-regional relapse. The first 200 patients ($\leqslant$ age 70 years) with operable stage I and II breast cancer diagnosed on fine needle aspirate have been analysed. Those in the adjuvant group received 6 months of chemotherapy together with tamoxifen (continued for 5 years) whilst 3 months of chemoendocrine therapy before and after appropriate surgery and radiotherapy was given as a neoadjuvant schedule. Overall clinical response rates for the latter have been high (85%), and at a median follow up of 28 months, only 4 patients have relapsed locally in either the breast (2 adjuvant, 1 neoadjuvant) or axilla (1 adjuvant). Lower rates of recurrence have occurred in the neoadjuvant group despite a greater proportion of positive pathological margins (28% neoadjuvant, 24% adjuvant). Tumour grade and extent of DCIS were similar for the two groups ($P > 0.05$), with significantly more rumours $\leqslant$2 cm present in the neoadjuvant group ($P < 0.001$). Chemoendocrine therapy may either reduce or delay local recurrence and perhaps undermine the significance of margin positivity. Moreover, prior exposure of cells within a primary tumour to neoadjuvant systemic therapy may modify the biological potential of any residual tumour cells and subvert the development of clinical recurrence.