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

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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

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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

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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

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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

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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.