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BCL-2 EXPRESSION IS RELATED TO METASTATIC POTENTIAL IN BREAST CANCER

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Bcl-2 is an oncogen that prevents programmed cell death (apoptosis). Bcl-2 expression has been reported in lymphoid malignancies as a result of t 14:18 and also in epithelial tumors like lung, prostate and skin cancers. The significance of Bcl-2 expression and its relationship with cell death in breast cancer has not been reported yet. We studied two groups of breast cancer samples, including 30 T1N1 and 28 T1N0 cases, looking for Bcl-2 expression in primary tumors and nodal metastasis. A monoclonal antibody anti-Bcl-2 , clone 124, from ICI, Cambridge Biochemicals Incorporated, was used in paraffin-embedded tissue sections stained by IHQ. Cytoplasmic expression of Bcl-2 protein was found in 43% of T1N0 and in 70% of T1N1 cases (p=0.08). A correlation with histological grade was also found: 89% of grade 1 tumors, 61% of grade 2 and 33% of grade 3 were positive. When Bcl-2 expression was compared to hormone receptor of tumor cells a good positive correlation with estrogen receptors (ER) and progesterone receptors (PR) was noted. In ER positive cases Bcl-2 expression was found in 80% of T1N1 and only in 55% of T1N0 (p=0.1). In PR positive cases Bcl-2 was detected in 92% of T1N1 and only in 30% of T1N0 (p=0.006). In situ DNA fragmentation using biotinylated poly dU binding, as a sign of apoptosis, was also studied in 12 cases. Bcl-2 negative cases showed a higher amount of positive cells. Our results suggest that Bcl-2 expression has an important role in breast cancer, favouring cell survival and therefore cancer progression, from early stages to the molecular events associated with metastatic invasion.

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DISTRIBUTION OF HLA-DRB ALLELES IN BREAST CANCER PATIENTS DIFFERS FROM THIS ONE IN HEALTHY DONORS

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Southern-blot study of 41 breast cancer (BC) patients and 120 healthy donors revealed the drastic increase of the occurrence of DRB homozygous genotypes (32% vs. 7,5%) and DRBw11 (DRB-5-1) allele (25% vs. 12%) in BC group. Presence of DRBw11 allele and homozygous genotype of BC patients were associated also with lack of deletions of chromosomal loci 11p, 17p and 17q (32,7% vs 14,7%, P<0,05; and 38,5% vs 17,6%, P<0,05 respectively). Some peculiarities of DRB genotype were correlated with size of tumour, nodal involvement and stage of disease. Clinical significance of such data can be discussed.

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WEEKLY EPIRUBICIN IN HORMONE-RESISTANT METASTATIC BREAST CANCER(MBC) IN THE ELDERLY.

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Identification of an active and well tolerated treatment for MBC refractory to hormonal therapy in elderly patients(pts) is presently a challenge for the Oncologist and deserves careful clinical research. From January 1988 to June 1992, we treated 17 pts over 70, affected by MBC, who had failed at least two lines of hormonotherapy. Median age was 74 years (70-81), median PS was 1 (1-3); the dominant site of metastatic disease was soft tissue in 5, bone in 5 and viscera in 7, eight pts bearing multiple sites. Treatment consisted in epirubicin 25 mg i.v. once a week, irrespective of body surface area, for at least 8 administrations. Fifteen pts are fully evaluable (1 early death, 1 refusal): we observed 1 CR, 4 PR, 5 NC and 5 PD; median time to progression for responders and NC pts was 9 months (6-21). As for site of metastasis we observed an objective response in 3/8 soft tissue, 2/8 bone and 3/7 viscera. In 208 cycles administered (range:2-30), no grade >2 hematologic and gastro-intestinal toxicity was observed; one case of reversible grade 3 cardiac toxicity occurred; alopecia was never seen. In conclusion, weekly epirubicin is an active and safe regimen for MBC in elderly women and should be strongly considered when pts are no more responsive to hormonotherapy.

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ACCELERATED-INTENSIFIED CEF CHEMOTHERAPY WITH THE SUPPORT OF GM-CSF AND ERYTHROPOIETIN (Epo). Venturini M, Del Mastro L, Garrone O, Danova M, Testore F, Latini F, Rosso R. IST Genova, Oncol. S.Matteo Pavia, Oncol. Asti, Scheringh-Plough Italia

Anemia and thrombocytopenia were main toxicities of accelerated (q.16 days) standard dose CEF+GM-CSF (Cyclophosphamide, Epidoxorubicin, Fluorouracil) (Venturini M, ASCO '92). In order to intensify this accelerated regimen, we started a phase I study, in advanced breast cancer patients, adding Epo (150 IU/kg 3 times per wk) to CEF (q.14 days) + GM-CSF (5 µg/kg/d, from day 3 to day 10).

The dose of F was fixed at 600 mg/m2 while the doses of C and E have been escalated as shown.

	Cohort					
Drug	1st	2nd	3rd	4th	5th	6th
E	70	80	90	100	110	120
C	800	1000	1200	1400	1600	1800

Preliminary results are here reported.

	1st (3 pts)	2nd (3 pts)	3rd (2 pts)
Mean n° of cycles	6	4.6	4.5
Mean interval (days)	17	16	18.7
Mean ARDI*	1.46	1.8	1.7

*ARDI= Average Relative Dose-Intensity compared to a CEF (600/60/600) q.21 days.

Grade (g) IV leukopenia was observed in 6/18 (33%), 10/14 (71%) and 4/9 (44%) cycles; g IV thrombocytopenia in 1/18 (6%), 1/14 (7%) and 1/9 (11%) cycles in the 1st, 2nd and 3rd cohort respectively. Only 2 episodes of g III thrombocytopenia were observed (2nd and 3rd cohort). No g IV anemia was recorded; g III occurred in 1 cycle both in the 1st and 2nd cohort; only 1 pt (2nd cohort) required blood transfusions. Early results of this ongoing trial suggest a beneficial hematological effect by associating GM-CSF+Epo as support to accelerated-intensified CEF regimen.

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DOSE-RESPONSE EFFECT TO EPIRUBICIN (EPI) IN PATIENTS (PTS) WITH ADVANCED BREAST CANCER (ABC). Vici P., Conti F., Di Lauro L., Venturo I., Paoletti G., Lopez M.; Regina Elena Institute for Cancer Research. Rome, Italy.

Although a dose-response effect to anthracyclines has been suggested in various tumors, concluding clinical evidence is still missing in ABC.We have conducted two consecutive trials with EPI at two dose levels (120 and 160 mg/m² q 3 weeks) in anthracyclines-naive ABC pts. EPI 120 mg/m². Characteristics of 45 pts: median age 51.5; median PS 1; previous adjuvant/advanced chemotherapy 12/11; dominant site of disease soft tissue in 10, visceral in 24, bone in 11 pts; n° of metastatic sites 1 in 19, 2 in 21, 3 in 5 pts. The median number of cycles was 6, the maximum cumulative EPI dose was 1200 mg/m². In 40 evaluable pts we observed 6 CR and 14 PR (50%); median duration of response was 7 months (mo), median time to response 2 mo, median time to progression 8 mo, median survival 21 mo. Toxicity: myelosuppression was mild, with G4 leukopenia in 7%, G3 in 38% of the pts, and only 1 EPI dose reduction. A transient asymptomatic decrease in LVEF ≥ 20% was recorded in 3 pts at a cumulative EPI dose of 720, 960, 1200 mg m². EPI 160 mg/m². Characteristics of 43 pts: median age 59; median PS 1; previous adjuvant/advanced chemotherapy 12/1; dominant site of disease soft tissue in 11, bone in 9, visceral in 23 pts; n° of metastatic sites 1 in 21, 2 in 17, 3 in 5 pts.The median n° of cycles was 6, the maximum cumulative EPI dose was 1280 mg/m². In 37 evaluable pts there were 4 CR and 18 PR (59%); median time to response was 2 mo; median time to progression, median duration of response and median survival are not reached yet. The dose limiting toxicity in 40 evaluable pts was leukopenia with neutropenic fever in 42% of the pts. This required a dose-reduction in 15 pts. Transient asymptomatic ≥20% LVEF decreases occurred in 3 pts, at a cumulative EPI dose of 640, 960 and 960 mg/m². Although not significant (P=0.54), the difference in response rate between the 2 trials suggests that a dose-response effect to EPI may exist, especially if one considers that the severe myelosuppression at EPI 160 mg/m² did not allow the delivery of the planned dose-intensity in 47% of the pts. Therefore, the study continues with EPI 160 mg/m² + G-CSF.