HIGH-DOSE CEF (CYCLOPHOSPHAMIDE, EPIRUBICIN, FLUOROURACIL) AS PRIMARY CHEMOTHERAPY IN LOCALLY ADVANCED BREAST CANCER: LONG TERM SURVIVAL DATA

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Purpose: To determine wether primary CEF is effective in locally advanced breast cancer, as measured by response, local recurrences, disease free survival (DFS) and overall survival (OS).

Patients and methods: From 1990 to 1998, 62 patients (pts) with stage III disease were enroled into a prospective study at Regina Elena Institute for Cancer Research, Rome. Inflammatory breast cancer (IBC) was included. Pts received three 21 d cycles of chemotherapy that consisted in epirubicin 50 mg/m^2, cyclophosphamide 400 mg/m^2 and fluorouracil 500 mg/m^2 i.v. on days 1 and 8. G-CSF (300 lg) was given subcutaneously every other day from days 5 to 17. After primary chemotherapy, whenever possible, mastectomy or conservative surgery was performed. Subsequently responding pts received the same regimen, whilst non-responders were given a non-cross resistant chemotherapy. In case of conservative surgery or initial T4 tumour radiation therapy was performed at the end of adjuvant chemotherapy. ER positive pts received tamoxifen 20 mg/d for five years.

Results: Median follow for the cohort was 109 months (range, 10–199). The local recurrence rate was 19.3%; two pts developed a new primary cancer in the contralateral breast. Distant metastases occurred in 29 pts (46.7%). The 5 years DFS rate for IIIA pts was 14.3% (median DFS: 27, CI 95% 17–37), for IIIB was 52.5% (median DFS: 87, CI 95% 10–175) for IBC was 20% (median DFS: 27 month, CI 95% 14–40), *p*-value 0.009. The 10-years OS for the IIIA pts was 28.6% (median OS: 43 month, CI 95% 30–56), for IIIB was 47.5% (median OS:116 month, CI 95% 47–185) and for IBC was 26.7% (median OS: 46 month, IC 26–66), *p*-value 0.11.

Conclusion: Ten years of follow up of stage III breast cancer is rarely reported. In IIIB pts we obtained a good local control and interesting long term data of OS.

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EXPERIENCE OF 170 CASES OF DUCTAL CARCINOMA *IN ' (DCIS)*

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Background: DCIS currently accounts for up 25% of all newly diagnosed breast cancers, but it can give rise to potentially lethal invasive carcinoma if undetected and left untreated. We are unable to predict which DCIS will progress to invasive cancer and the time interval to the development of recurrent DCIS or invasive carcinoma.

Methods: Retrospectively one hundred seventy patients (pts) with DCIS of the breast were observed between 1996 and 2007 in our Institution. The main characteristics of these pts included: median age 53 years (range 23–78); menopause 112 pts (66%); fertility 139 pts (82%); surgery: mastectomy 39 pts (23%) and local excision 131 pts (77%). After breast-conserving treatment (BCT) 123 pts (94%) received radiotherapy. Overall, 72 pts (42%) received tamoxifen.

Results: With median follow-up of 56 months (range 4–71), recurrence rate was 4.7% (8 pts: 5 ispilateral; 2 controlateral and 1 ipsilateral + controlateral synchronous). Median relapse free survival was 45 months (21–87). Approximately 75% of the of these recurrences have developed invasive cancer and 25% DCIS. All pts had more than 40 years (6/8 between 40 and 50 years) and underwent BCT. The initial histological characteristics of these women were: 7/8 comedo carcinoma and 6/8 presence of disease at the surgical margins. Seven of these pts underwent breast irradiation (87.5%) and only three pts (37.5%) hormonal therapy with tamoxifen. The overall survival of all group was 95.3%.

Conclusions: These retrospective data confirmed that mastectomy treatment is associated with optimal local control. Pts with age between 40 and 50 years and comedocarcinoma histology might be considered at high risk of local recurrence.

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NUOVO RUOLO DEGLI INIBITORI DELL'AROMATASI: IMPIEGO IN TERAPIA ADIUVANTE

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Il trattamento ormonale ha l'obiettivo di impedire che gli estrogeni possano legarsi ai recettori ormonali: requisito fondamentale a tutti i tipi di manipolazione ormonale è dunque l'espressione da parte delle cellule tumorali dei recettori per gli estrogeni e/o per il progesterone.

Le opzioni terapeutiche sono diverse: in premenopausa è necessario abolire l'attività ovarica con i farmaci agonisti LH-RH, che portano alla soppressione della produzione di estrogeni mediante interferenza con l'asse ipotalamo-ipofisi, con conseguente ipogonadismo di origine centrale (castrazione medica); a questi va associato il tamoxifen, che compete con gli estrogeni prodotti in sede extraovarica per il legame con i recettori.

In menopausa il tamoxifen era la terapia standard fino a qualche anno fa, ma negli ultimi anni è stata sviluppata una nuova categoria di farmaci, gli inibitori di terza generazione dell'enzima aromatasi (anastrozolo, letrozolo, exemestane); l'aromatasi è l'enzima responsabile, in menopausa, della conversione degli androgeni surrenalici in estrogeni: questa avviene a livello periferico, cioè osso, fegato, muscolo, tessuto adiposo, tessuto tumorale mammario. Mentre il tamoxifen è un farmaco ampiamente usato da più di 30 anni e quindi ben conosciuto, gli effetti a lungo termine degli inibitori dell'aromatasi sono per certi versi ancora non del tutto noti.

Il tamoxifen per 5 anni costituiva fino a pochi mesi fa il trattamento standard: complessivamente l'ormonoterapia con tamoxifen era in grado di diminuire il rischio di recidiva del 37–54% e di diminuire il rischio di morte del 10–33%. Tuttavia i recenti studi con gli inibitori dell'aromatasi in donne in menopausa hanno evidenziato come questi farmaci siano in grado di migliorare ulteriormente la sopravvivenza libera da malattia, e, in alcuni studi, la sopravvivenza globale.

In particolare le strategie valutate sono state: (1) l'inizio del trattamento ormonale con inibitore dell'aromatasi per 5 anni (up-front) (anastrozolo, studio ATAC; letrozolo, studio BIG 1-98); (2) l'inizio di un inibitore dell'aromatasi dopo 2-3 anni di tamoxifen (early-switch), fino ad un totale di 5 anni di ormonoterapia (exemestane, studio IES; anastrozolo, studi ABCSG trial 8/ARNO 95; letrozolo, studio BIG 1-98, i cui risultati non sono ancora stati pubblicati); (3) il proseguimento del trattamento ormonale oltre i 5 anni, con switch dopo 5 anni di tamoxifen a letrozolo (late-switch-studio MA 17).

Sulla base di questi studi l'ormonoterapia con tamoxifen non rappresenta più il gold standard: sia la Consensus Conference di San Gallo che l'American Society of Clinical Oncology raccomandano infatti l'utilizzo di un farmaco inibitore dell'aromatasi (up-front oppure early-switch) in tutte le pazienti con tumore ormonosensibile.

Sull'uso degli inibitori dell'aromatasi nel trattamento adiuvante restano ad oggi alcune questioni aperte, alle quali daranno risposta gli studi in corso:

Esiste un anti-aromatasico più efficace degli altri?

È meglio un trattamento up-front oppure uno switch precoce? Sicuramente lo switch precoce potrebbe mettere al riparo dalla tossicità long-term del tamoxifen e sfruttarne invece le caratteristiche benefiche estrogeno-agonista sull'osso (protezione da osteoporosi) e sistema cardio-vascolare, mentre l'anti-aromatasico up-front è più efficace nel ridurre il rischio di recidiva e/o morte, quanto meno in pazienti ad alto rischio di ricaduta, nelle quali il tasso di ricaduta è maggiore nei primi 2 anni;

Nel caso di switch precoce, qual è la durata ottimale dell'inibitore dell'aromatasi (3 o più anni)?

Siamo autorizzati, nella scelta della strategia terapeutica, a tenere conto dello stato di HER2-neu? Probabilmente sì, infatti e stato dimostrato che le pazienti con HER2 iperespresso sono maggiormente avvantaggiate dall'uso di un anti-aromatasico;

Sono altrettanto efficaci nelle donne con menopausa indotta farmacologicamente? Gli studi sono in corso e i risultati saranno pubblicati nei prossimi anni.

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METRONOMIC ORAL VINORELBINE AND TEMOZOLOMIDE, AFTER WHOLE BRAIN RADIOTHERAPY, FOR THE TREATMENT OF BREAST CANCER PATIENTS WITH BRAIN METASTASIS. A PHASE II STUDY

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Background: The incidence of Central Nervous system (CNS) metastases has been reported to be 15–25% in patients with breast cancer. Temozolamide (TMZ) is a new orally administered imidazo-tetrazine with proven activity in Brain metastasis. Vinorelbine The recently introduced oral form of this vinca alkaloid derivative, Vinorelbine, has disclosed new and useful perspectives particularly for elderly patients.

Methods: Patients with breast cancer and newly diagnosed, inoperable, brain metastases (BM) were eligible. We have treated 19 consecutive patients (mean age: 55.2 $\pm$ 22.4 years; median age: 57.9 years) affected by brain metastases with WBRT at 3 Gy/d administered over a two-week period (on weeks 1–2), total dose 30 Gy, and an induction with TMZ 75 mg/m^2/d during this period, followed by 4 weeks off-therapy and subsequent original schedule with TMZ administration at 75 mg/m^2 on days 1–21 every and oral Vinorelbine (VNR) 70 mg/m^2 fractionated in days 1, 3 and 5, one week on-one week off, every four weeks up to 12 cycles.

Results: All patients were subjected to the induction therapy. Two grade three, 12 grade II and 10 grade I neutropenia (CTC), 5 grade II anaemia, seven grade I and four grade II thrombocytopenia and nine grade I alopecia were recorded. Fourteen grade I and 7grade III, nausea and vomiting were observed, moreover, liver or renal toxicity were never recorded in our series being the schedule well tolerated in all patients. two CR (10%), and 8 PRs (42%) were recorded whilst a clinical benefit was achieved in other four patients (21%). The Objective Responses rate was 52% (C.I. 42.7–64.9%), whilst the disease control rate was 73% (C.I. 61.7–82.4%). Overall survival was 59% at 1 year.

Conclusions: These preliminary results show that some of the pts who received complete treatment plan could achieve prolonged disease control and survival. The schedule was safe and well tolerated (also in old pts.) and has suggested an encouraging activity in brain metastases from breast cancer.

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A METRONOMIC TREATMENT WITH ORAL CHEMOTHERAPY IN PATIENTS ELDERLY WITH METASTATIC BREAST CANCER

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Clinical observation evidence that continuos administration of small dose chemotherapy (metronomic dosing scheme) has the possible advantage of better tolerability and efficacy for a wider range of cell population.

The aim of our study is to evaluate the efficacy of a metronomic oral schedule of Idarubicin and Capecitabine in patients elderly with metastatic breast cancer pre-treated with chemotherapy (no response to three sequential regimens) and non more to hormonotherapy responsive.