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DEXVERAPAMIL TO OVERCOME ANTHRACYCLINE-RESISTANCE IN ADVANCED BREAST CANCER

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Calcium-channel blockers are able to overcome the P-glycoprotein related multi-drug-resistance (MDR 1) of tumors *in vitro* and *in vivo*. Dexverapamil (DVPM), the R-enantiomer of verapamil, has shown similar potency in reversing MDR1 in tumors as the S-enantiomer, but had a 5 to 10-fold lower cardiac activity. Since 6/92 41 patients (pts) with advanced breast cancer were treated in a multicenter-study with epirubicin (E) 120 mg/m^2 every three weeks. In case of progression (PD) or no-change (NC) after 2 cycles, E was continued with the same dose but supplemented with 4 × 300 mg DVPM daily, starting 2 days before E-therapy for a total of 13 doses. Up to now 20 pts received treatment with E plus DVPM and 14 of them are evaluable for toxicity and activity: Median age 55 years (35–65). Hormonreceptor-status: 7 positive, 5 negative and 2 unknown. 11/14 pts have had at least 1 chemotherapy before epirubicin-treatment; 11 pts presented with visceral metastases; in 8 pts metastatic disease involved more than 3 sites.

Toxicity-grade	(WHO)	E	E plus DVPM
WBC	3/4	6	7
Platelets	3	0	1
Anaemia	2	2	4
Mucositis	2	1	3
Pulse-frequence	<60 ... >40/min	2	8
RR syst.	<90 ... >80 mmHg	0	5
AV-block	1st degree	2	6

In 7 pts single-dose of DVPM was escalated up to 350 mg, in 2 pts dose of DVPM was reduced to 250 mg because of drop in systolic blood pressure below 80 mmHg.

In 2 of 14 pts addition of DVPM was capable of including partial remission (1 PD site E, 1 NC after E). 9/14 pts showed NC after adding DVPM to E-treatment (6 NC after E, 3 PD after E). The preliminary data showed that adding DVPM to E is feasible with managable toxicity. In some pts it is possible to overcome epirubicin-resistance by E plus DVPM.

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AMINOGLUTETHIMIDE + HIDROCORTISONE (AMG + HC) VS. MEGESTROL ACETATE (MEG) AS SECOND AND THIRD LINE TREATMENT IN ADVANCED BREAST CANCER (ABC): A PHASE III STUDY

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From Nov 84 to Sept 93, 157 patients (pts) with ABC were randomized to receive MEG 160 mg daily p.o. (79 pts) or AMG 500–1000 mg + HC 40 mg daily p.o. (78 pts) and stratified according to previous response to tamoxifen, free interval and time since menopause. There were no significant differences in the distribution of the most important prognostic factors except in the bone metastases (AMG 38, MEG 44; $P = .05$) and soft tissue (AMG 24, MEG 12; $P = .06$). The responses in the AMG arm were (%): CR 6, PR 19.7, NC 50, PD 24 and in the MEG arm 3, 17, 44 and 35 ($P = .54$). Median (M) time to progression (tp) was 211 days (4–2045) for AMG and 193 (14–1247) for MEG. M survival (s) time was 720 d (60–2160) and 600 (30–1860) respectively. The curves of tp and s (Kaplan-Meier) were super-imposable. Six pts withdrawn from the AMG and 1 from the MEG due to toxicity. Twenty-six pts in the AMG arm had toxicity G 3–4 and 8 in the MEG arm ($P = .001$). After progression 39 pts changed to MEG and 47 to AMG. Responses were (%): with MEG 10 PR, 29 NC, 59 PD; with AMG 2 CR, 4.7 PR, 39 NC and 53 PD. **In conclusion,** although the response rate with AMG was slightly higher than with MEG, we cannot disregard the hypothesis that both arms are similarly active. Also since tp and s curves are similar, this supports the possibility that both treatments have the same efficacy. The toxicity with AMG (1 gr) is higher than with MEG.

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EVALUATING THE SOCIO-ECONOMICS OF CHEMIOTHERAPIC AGENTS IN BREAST CANCER: THE FRENCH PERSPECTIVE

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A Markov process model was designed to evaluate the socio-economic of new therapeutic agents for second-line therapy of metastatic breast cancer. The model is based upon 28 disease states for responses (PR, CR, NC, PD, EPD), toxicities (minor, acute, cumulative) and diseases complications. Utilities were estimated using the standard gamble technique from a survey involving 20 French oncology nurses from 2 hospitals and 1 outpatient clinic as proxy patients. Health status was validated from interviews with 5 French oncologists and 3 oncology nurses. Transitional probabilities, based on phase II trials reports, were calculated using the actuarial method and a density function approach.

Evaluation of costs was conducted from the combined view points of the Health Care System and of the patient. Direct non medical and indirect cost were excluded from the calculation. DRG reimbursement rates were used as a proxy for hospital cost of the therapy. Linkage per patient of the successive hospital stays was obtained by examining the medical records of 153 patients in 5 different sites. Outpatient costs, were estimated on the basis of the prescriptions made for the patient at discharge from hospital. Assignment of monetary cost lay upon the French relative value scale and retail prices.

Assessment of cost and quality of life under treatment from the beginning of the chemiotherapy until death has been carried out under this methodology.

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LONG-TERM SURVIVORS AFTER CHEMOTHERAPY (CT) IN METASTATIC BREAST CANCER (MBC). A RETROSPECTIVE STUDY

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From a data base of 1724 patients (p) with MBC, we selected a group of 612 p (35.5%) treated with CT as only first-line treatment. CT was chosen in the basis of clinical criteria.

There were 609 women (99.5%), with mean age of 50 years (range 24–89). Forty-eight percent had received adjuvant treatment after the local treatment of the primary (median of disease free survival until metastatic disease: 14 months (m), range 0–180) and a 73%, (447 p) had suppressed ovarian function.

Metastatic disease was present in an isolated organ in 48%. of p. Lymph-node involvement was present in 43% of p, skin in 39%, lung in 45% (34% nodular and 11% lymphangitic), bone in 28%, pleura in 18%, liver in 11%, brain in 2% and other organs in 2%.

Overall response rate was 36.6% (13.4% CR and 23.2% PR). There were no changes (NC) in 21.7% and progressive disease (PD) in 41.7%. With a median follow-up for CR of 6 m (2–192), 65 p (79%) have relapsed. Median duration of CR was 20 m (CI 95% 16–24). Most of relapsed patients received a second line treatment.

After a median follow-up for survival of 14 m (2–219), 439 p (68.5%) have died. Median survival (and 95% CI) were 20 m (18–22) for the whole series, 42 m (29–53) for CR, 21 m (17–25) for PR, 24 m (19–29) for NC and 11 m (9–13) for PD. There were statistically significant differences in survival between CR vs PR, CR vs NC, CR vs PD, PR vs PD and NC vs PD.

In conclusion we have observed long survival in selected patients who obtain CR after standard doses of CT.