Round Table

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High-dose chemotherapy in breast cancer. The Dutch trial

E.G.E. de Vries, M. Bontendal, L.V.A.M. Beex, E. van der Wall, D.J. Richel, M.A. Nooij, E. Voest, P. Hupperets, A.M. Westermann, O. Dalesio, S. Rodenhuis. *The Netherlands Working Party on Autologous Transplantation in Solid Tumors; Department of Medical Oncology, University Hospital Groningen, The Netherlands*

The study of the Dutch Working Group on Autotransplantation in Solid Tumors closed in 1999 and randomized 885 patients. About one-third of these patients had 10 or more tumor-positive axillary lymph nodes, the remainder of patients had 4–9 positive axillary lymph nodes. Patients were randomized following definitive surgery to receive either 5 courses of fluorouracil, epirubicin and cyclophosphamide, followed by radiation therapy and tamoxifen or to the same sequence in which the 5th course FEC was replaced by high-dose chemotherapy with cyclophosphamide, thiotepa and carboplatin. This high-dose regimen is similar to the CTCb (STAMP V) regimen, but it contains a double dose of carboplatin and the 3 alkylating agents are infused as short term intravenous infusions rather than as continuous infusions. This may lead to less inhibition of the activation route of cyclophosphamide than the continuous infusion employed in the CTCb regimen. The mortality rate was only 1%. For the whole group there was in 2000 no statistical significant difference for disease free survival at 3 years with 72% in the high-dose and 65% in the conventional dose arm. A separate analysis of the first 284 patients with a median follow up of 53 months revealed a 3-year disease free survival of 77% in the high-dose arm versus 62% in the conventional dose arm ($p = 0.009$), and a 3-year overall survival of 89% versus 79% ($p = 0.039$). The Dutch study was performed in 10 centers. There was no cross-over from the conventional-dose arm to the high-dose arm and less than 10% treatment refusals among patients randomized to the high-dose arm. The relapse-free and overall survival results of the Dutch study need further maturation. Meaningful statistical analysis is anticipated for the year 2002.

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The French trials

Abstract not received.

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The Scandinavian Breast Group Study SBG-9401 comparing tailored and dose-escalated FEC (tFEC) with marrow supported high dose therapy (CTCb) in the adjuvant setting for high risk breast cancer

J. Bergh. *SBG-9401 Study Group, Karolinska Hospital, Department of Oncology, Stockholm, Sweden*

Between March 1994 and March 1998 525 women with high risk primary breast cancer were randomly allocated after primary surgery to tFEC or CTCb. tF300-600E38-120C450-1800 was delivered for 9 courses with individually adapted doses based on haematological tolerance. The nine courses of tFEC were given with G-CSF (filgrastim) and prophylactic antibiotic support. In the CTCb-arm patients received 3 courses of standard F600E60C600. The last FEC course was given with cyclophosphamide at 1200 mg/m2 supplemented with G-CSF (filgrastim) to facilitate harvest of peripheral stem cells. CTCb was given at 6000 mg/m2, 500 mg/m2 and 800 mg2 as a continuos infusion for 4 days. Patients in both arms received loco-regional radiation and tamoxifen for 5 years. Patients quality of life was evaluated at regular intervals by the EORTC QLQ-C30 during the first years. At the median follow-up for relapse of 34.3 months there was a statistically significantly benefit for the tFEC group, 81 relapses versus 130 relapses ($p=0.04$, double triangular method). There was no statistical difference in overall survival, 60 deaths in the tFEC group and 82 in the CTCb group (log rank $p=0.12$). Statistically significantly more acute toxicity was registered in the CTCb arm. Ten patients have developed AML or MDS in the tFEC arm. Quality of life deteriorated markedly and deeper for the CTCb arm but returned quicker to normal compared with the tFEC arm, which had a longer therapy duration. At around one year after diagnosis quality of life parameters essentially had returned to the values recorded at time of inclusion for both arms. FEC is a highly potent regimen with manageable acute side-effect but with an increased risk for AML/MDS which require refinement of tFEC aiming at reducing this risk.

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A randomized trial of high-dose chemotherapy (HDCT) with autologous peripheral blood stem cell support (asct) compared to standard chemo therapy (ct) in women with metastatic breast cancer: a National Cancer Institute of Canada (NCIC) clinical trials group study

S. Gluck[1], M. Crump[2], D. Stewart[1], M. Levine[2], K. Pritchard[2], P. Kirkbride[2], J. Dancey[2], S. O'Reilly[2], T. Shore[2], S. Couban[2], C. Girouard, H. Abuzara, D. Tu, S. Martin, L. Shepherd[2]. *[1] University of Calgary, Tom Baker Cancer Ctr.Clinical Research Programme, Calgary, Alberta, Canada; [2] National Cancer Institute of Canada, Clinical Trials Group, Kingston, Ontario, Canada*

Introduction: In April 1997 we initiated a multi-centre, randomized trial to compare overall survival and quality of life of women with chemosensitive metastatic breast cancer treated with 6 cycles of standard induction chemotherapy and then either one consolidation treatment with HDCT + ASCT or continued standard-dose therapy.

Demographics: Between 7/1997 and 12/2000, 386 patients were registered, and 224 randomized: 112 to HDCT + ASCT and 112 to standard CT. Median age was 46 and 47.8 yrs; 32% hormone receptor neg., 31% progressed on/after prior Tam, 30% HR+ and no prior Tam; 67% received anthracycline based induction therapy and 33% taxane based. Complete remission rates prior to randomization were 11 and 12% respectively.

Results: 55 deaths in each arm were observed. 7 (6%) patients on the HDCT arm died of toxicity. The intent to treat analysis resulted in a median overall survival of 1.98 years for HDCT and 2.31 years for standard treatment (95% CI 1.7 - 3.18 and 1.55 - 2.55). The hazard ratio for survival is 1.011, $P = 0.96$. The progression free survival analysis revealed a hazard ratio of 1.486 (95% CI 1.080 - 2.046) in favor of HDCT. For this analysis there were 69 (62%) events vs. 84 (76%) events, $P = 0.01$. Of all patients, 21% did not receive the HDCT due to progression of disease or withdrawal of consent.

Conclusion: The MA16 study indicates that HDCT as given in our study does not improve survival for patients with metastatic breast cancer when used as consolidation treatment after 6 cycles of induction chemotherapy.

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High-Dose Chemotherapy for Breast Cancer: US trials

S. Bearman. *University of Colorado Health Sciences Center, Bone Marrow Transplant Program, Denver, USA*

High-dose chemotherapy (HDCT) for breast cancer is probably the most controversial oncologic treatment today. After numerous phase II studies showed significant promise for this approach, prospective randomized trials were initiated in the United States and Europe. Four phase III studies have been conducted in the United States addressing the role of high-dose chemotherapy in the treatment of breast cancer. These include: PBT-01, which compared HDCT with conventional dose chemotherapy for patients with metastatic breast cancer; CALGB-9082 and ECOG-2190, both of which evaluated HDCT for patients with primary breast cancer and 10 or more involved axillary nodes; and SWOG-9623, which studied HDCT in primary breast cancer patients with 4 or more involved nodes. The results of PBT-01 have been reported in the literature. Preliminary analyses of CALGB-9082 were reported at the 1999 and 2001 meetings of ASCO. The 2001 ASCO