Round Table

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High-dose chemotherapy in breast cancer. The Dutch trial

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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

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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

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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

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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

presentation was reported with 90% of the expected events having occurred in the non-transplant arm. The final analysis of CALGB-9082 is not expected to be significantly different than the recent ASCO presentation. ECOG-2190 completed accrual in 1999 and the data are expected to be mature in the summer of 2002. SWOG-9623, the only US study in patients with 4 or more involved axillary nodes and the only study which incorporated a taxane in the non-transplant arm, was closed in February of 2001, due to poor accrual after the 1999 ASCO meeting. A total of 602 patients out of an intended 1000 were enrolled. The designs of each study will be reviewed, as will the results which have been published or presented to date. How these studies have been interpreted and presented will be critically discussed.

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Avoidance of cystectomy in carcinoma in situ

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CIS of the bladder is a high-grade lesion recognized as a morphologic entity. Bladder irritability is the leading symptom in patients with primary CIS. Exfoliative urinary cytology is the most important diagnostic tool. Biopsies have to be taken from suspicious areas, preselected sites in the bladder and from the prostatic urethra. While cystectomy was the initial treatment of choice, the high response rate to intravesical BCG justifies a more conservative approach to management. The complete response rate with BCG immunotherapy is $\geq$70%. Patients not responding to BCG immunotherapy without evidence of progression may be treated with alternative immunotherapies such as alpha-2b interferon, keyhole limpet hemocyanin (KLH) or bropirimine, with intravesical chemotherapy or photo dynamic therapy. If treatment is ineffective, cystectomy should not be delayed for more than 6 months. Further studies with long-term observation will be warranted to elucidate the natural history and to identify prognostic factors of CIS of the bladder.

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Biological selection for organ conservation

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Bachground: Clinical criteria helpful in determinating patients for bladder preservation include such variables as small tumor size and a possible complete transurethral resection (TUR) prior to radiochemotherapy (RCT). Tumor heterogeneity, however, is so great in bladder cancer that conventional histopathologic classification is inadequate for predicting the response to RCT for individual lesions. Molecular markers that may predict a tumor's true malignant potential as well as its response to specific cytotoxic therapies are sorely needed.

Methods: Several markers have been linked to radio- and chemosensitivity of bladder cancer cells, including p53, pRb, cyclin D1 and bcl-2 as key protein regulators of the cell-cycle and the apoptotic pathway. We and other groups have evaluated these biological markers as possible predictors for response to RT/RCT and as prognosticators for local control with preserved bladder.

Results: In an analysis of 70 patients treated uniformly within our bladder sparing protocol of TUR and RCT, we found the spontaneous apoptotic index (AI > median) and the proliferation rate (Ki-67 > median), but not the p53- and bcl-2 expression, to be significantly related to inital response and local control with preserved bladder at five years. In an exploratory multivariate analysis, which included clinicopathological and molecular factors, only AI, Ki-67 and the combined AI/Ki-67 variable retained significance for local control with preserved bladder at five years. Other groups have confirmed the predictive value of a high spontaneous AI for response to RT/RCT, however, the role of the various apoptosis-related regulators is often contradictory and their interrelationship needs to be further elucitated.

Conclusion: We anticipate that translational research will help to predict treatment response of bladder tumors and, thus, to tailor individually adjusted therapy. However, only a multi-parametric assay will allow early choice of the best treatment regimen and therefore avoid unnecessary morbidity associated with cystectomy or RCT. Then, both strategies would no longer be competitive, but complementary.

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Chemotherapy in organ preservation in muscle invasive bladder cancer

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Neo-adjuvant chemotherapy was designed in order to treat micrometastatic disease, found in up to 50% of patients at presentation. Implications of bladder preservation are less surgery, no need for a urinary diversion and a normal sexual life. Quality of life should be improved. Bladder preservation is possible in selected patients, and can be safely achieved with neo-adjuvant chemotherapy implemented by definitive local treatment such as radiotherapy (RT), partial cystectomy, or TURB.

The combination of neo-adjuvant chemotherapy and RT produces overall 5-year survival rates from 42% to 63%, with organ preservation in approximately 40% of patients. With the advent of neo-adjuvant chemotherapy the indications for partial cystectomy have been expanded to: a) attain a clinical CR or significant PR to neo-adjuvant chemotherapy; b) who have solitary lesions in favorable anatomical locations; c) no carcinoma in situ; d) with no history of previous or recurrent infiltrative bladder cancer; and e) who have a good bladder capacity.

Neo-adjuvant chemotherapy and TURB alone have also been used: In selected patients survival is similar to that attained with radical cystectomy. There is interest in molecular markers to optimize therapy and predict chemo-sensitivity. Molecular markers such as p53 Rb, p21 and EGFR have been evaluated in bladder cancer.

Bladder sparing in patients in patients selected on the basis of response to neo-adjuvant chemotherapy is a feasible though controversial approach, as radical cystectomy is regarded as the gold standard of treatment. Bladder Prognostic factors should be studied to evaluate those patients most likely to benefit from this approach.

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Altered fractionation in chemo-radiation for bladder cancer

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To improve the results obtained by cystectomy (CT) alone and to specify the place of a conservative treatment in invasive bladder cancer, we designed a prospective study using a neoadjuvant 5FU-CDDP regimen with bifractionated split course radiation therapy followed by CT or additional chemo-radiotherapy. One hundred twenty patients (pts) with operable tumor were treated from 02/88 to 11/95 (52 T2, 31T3a, 37 T3b-T4). All patients underwent an initial trans-urethral resection with complete macroscopic debulking in 63 pts and received the neoadjuvant program. The neoadjuvant dose was 24 Gy delivered in 8 fractions over 17 days, according to a modified bifractionated split course schedule. Each fraction delivered 3 Gy twice on day D1, D3, D15 and D17. The pts received concomitant CDDP (15 mg/m^2) and 5-FU (400 mg/m^2) on day D1, D2, D3 and D15, D16, D17. A control cystoscopy and resection was performed 6 weeks later. Pts with persistent tumor uuderwent a CT. Complete responders were treated by additional chemo-radiotherapy. Ninety three pts (77%) achieved a complete histological response (CR) after the neoadjuvant program. Twelve pts developed a local recurrence (including 3pTa and 3pT1). Metastatic disease was seen in 28 pts, more frequently in non responder pts (63% vs 12%; $p < 0.0001$). The five-year survival was 63%, significantly better for responders (73% vs 29%; $p < 0.0001$). Definitive results will be presented. Others schedules with altered fractionation will be compared and discussed.