next "generation" of prognostic factors has been characterized by better measurability and reproducibility and therefore a higher degree of objectivity as e.g. morphometric criteria such as mean nuclear area (MNA), volume percentage of epithelium (VPE) or proliferation criteria such as mitotic index, DNA-index or S-phase fraction. Representants of the latter have proven to be of independent prognostic value when simultaneously tested together with new molecular targets. No definitive positioning and sometimes even contradictory data are available yet regarding the new prognostic markers: anemia, thrombocytosis, alpha-catenin, collagen IV, VEGF, tumor vascularity, IL-12, IL-6, CSF-1, PgR, CASA, sialyl-TN, p53, p21, CD 44v6, Bcl-2, c-erb B-2, p 27 KIP1, HSP 27, K-ras mutants, MCP-1, PDGF-alpha, uPA, uPAR, PAI-1, PAI-2 or clonogenic growth. Factors predictive for therapy have not been elaborated more conclusively as yet and comprise the following: chemosensitivity in vitro, p53, Bcl-2, c-erb B-2, INT-2, P-gp, MRP, LRP, excision repair, laminin expression, GSTpi, BAX and nm23. A critical appraisal with regard to the actual status of the single factors and their putative interrelationship discriminating prognosis and prediction will be presented.

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Prognostic implications of tumor cell infiltration of the hematopoietic system in pediatric and adult tumor patients

P.F. Ambros[1], G. Mehes[1], A. Luegmayr[1], A. Witt[2], E. Kubista[2], C. Hattinger[1], T. Lörch[3], I.M. Ambros[1], H. Gadner[1]. [1]*C.C.R.I., St Anna Kinderspital/Tumorcytogenetics, Vienna;* [2]*University Hospital, Vienna;* [3]*MetaSystems, Altlussheim, Austria*

In order to create a more individualized therapy, worldwide efforts exist to better define biological risk groups. Circulating tumor cells in the hematopoietic system could serve as important prognostic markers, however, the data available so far are controversial. This fact can be explained by biological differences between the individual tumor entities but could also be based on methodical problems. In carcinoma patients, the presence of tumor cells in the bone marrow (BM) and peripheral blood (PB) at diagnosis is believed to reflect a worse prognosis in patients with "localized" disease as compared to patients without BM involvement. Moreover, the prognostic effect of the dynamics of BM or PB clearing during the course of the disease was demonstrated for neuroblastoma and ALL patients by different reports. In order to circumvent diagnostic errors or problems caused by fluctuations of the mRNA or protein expression of the tumor cells, a method combining the detection of tumor-specific immunological and DNA aberrations was developed allowing the visualization of tumor cells (e.g. neuroblastomas, Ewing tumors and breast carcinomas) in a hematopoietic surrounding. In addition, this system allows for the first time to exactly quantify the number of infiltrating tumor cells. The sensitivity of this method is set by the cells available for analysis, thus allowing the unambiguous identification of extremely low tumor cell infiltrates (e.g. 1 tumor cell in 107 MNCs). In stage 4 NB patients with genetically aggressive tumors, we observed that the delayed tumor cell clearance of the bone marrow indicates a more serious development of the disease. Rapid bone marrow clearance seems to be associated with a decreased risk of death (RR = 0.09; 95% CI: 0.008–1.068). Thus, this new method allows both, an accurate diagnosis, quantification and functional characterization of low tumor cell infiltrates in the hematopoietic system besides offering an ideal way to monitor the response of the tumor cells to cytotoxic treatment.

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New prognostic factors in childhood cancers

O. Delattre[1]. [1]*Institut Curie, U 509 INSERM, Pathologie Moleculaire des Cancers, Paris, France*

Cytogenetic and molecular analysis of childhood cancers has lead to the identification of a number of genetic markers which are becoming instrumental for the management of patients. In Ewing tumour (ET), the presence of specific fusion genes between EWS and various members of the Ets family constitutes a tumour specific marker which can be used for the diagnosis of ET. Depending on the type of fusion transcript which is observed in the tumours, authors have suggested that this marker could also have a prognostic significance, the more frequent EWS-FLI-1 type 1 fusion being of better prognosis than other fusion types. The extreme sensitivity and specificity of the detection of this gene fusion has enabled to develop assays for a better evaluation of minimal metastatic disease in ET. Indeed, preliminary results indicate that micrometastatic patients with otherwise localized tumours share the same unfavourable outcome than patients with clinically detectable metastasis. In alveolar rhabmyosarcoma, a specific fusion between the PAX3 or 7 gene with FKHR is observed and similar assays for diagnosis and detection of micrometastasis are currently being developed. In neuroblastoma, the N-myc amplification, the loss of 1p chromosome fragment and the over-representation of 17q, constitute three genetic alteration which are frequently associated, and which have been shown to distinguish a particularly aggressive group of neuroblastomas. Finally, the clinical significance of mutations of the hSNF5/INI1 gene, a gene recently shown to be the target of loss-of-function mutations in malignant rhadboid tumours, among paediatric cancer will be discussed.

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High dose chemotherapy with hematopoietic stem cell support (HDCT) in germ cell cancer (GCC)

S.D. Fosså, A. Fosså. *The Norwegian Radium Hospital, Oslo, Norway*

Background: Even after the introduction of dose-intensified and drug-alternating cisplatin based conventional chemotherapy (CT), the 5 year survival rates for patients (pts) with intermediate and poor prognosis GCC remain 70% and 45%, respectively. In pts failing initial cisplatin based CT, conventional salvage treatment leads to a 30% long-term survival rate. Further dose intensification of the CT by HDCT has been introduced as a new treatment option for GC. In most schedules HDCT is applied by 1, 2 or 3 high dose cycles after 1 or 2 conventional courses of CT.

Results: In GCC HDCT has been evaluated as part of the primary treatment in pts with poor prognosis (risk assessment based on initial disease manifestations or on insufficient early decline in tumor markers) and in pts failing primary CT. Based on phase II studies long-term survival rates are 70–80% in pts with poor prognosis who receive HDCT as part of their primary treatment. In pts with relapsing/progressive disease long-term survival rates after HDCT are 0–50%, dependent on prognostic factors (degree of cisplatin-responsiveness, metastatic burden). In experienced institutions the overall toxic death rate is <5%. Currently ongoing phase III studies aim to confirm the above promising phase II results of HDCT (EORTC 30974, US Intergroup study, European study IT94).

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High-dose chemotherapy for solid tumors – The Spanish experience

H. Cortés-Funes. *For de SOLTI Group; Hospital Universitario "12 de Octubre", Madrid, Spain*

The SOLTI Group (Spanish Cooperative Group for the Study of Intensive Chemotherapy Treatment in Solid Tumors) was created in 1993. Originally comprising four centers, today the Group has eleven participating hospitals. At the time of its inception, the Group initiated five confirmatory studies in high-risk breast cancer patients using conventional high-dose chemotherapy regimen with peripheral blood progenitor cell (PBPC) support. Three of this studies have now been concluded and the remaining are due to the end of this year. The Group has already embarked on other new studies and other are being proposed for breast cancer and other solid tumors. At the end of 1998, 8 studies are ongoing and a total of 666 patients were enrolled.

Ongoing Studies: Patients with more than four positive and less than ten axillary nodes were included since april 1997 in a randomized *study 9606* designed to evaluate the use of adjuvant conventional accelerated doses of chemotherapy with or without high-dose as consolidation. Patients were allocated to receive four two-weekly cycles of epirubicin 120 mg/m^2 and cyclophosphamide 1 g/m^2 supported by G-CSF, followed or not by STAMP-V. Patients with 10 or more axillary lymph-nodes positives were included in *protocol 9701* replacing the original 9301 closed on April 1998. On this protocol patients receive two courses of doxorubicin, 80 mg/m^2 followed by two courses of paclitaxel 200 mg/m^2 every two weeks supported with GCSF, followed by one course of cyclophosphamide, 3 g/m^2 and paclitaxel 200 mg/m^2 with GCSF for stem-cell mobilization. After recovery patients receive STAMP-V consolidation.

The *Study 9608* investigate the use of paclitaxel given in weekly schedule at 80 mg/m^2 in patients relapsing after high-dose adjuvant treatment Forty patients were included and in a preliminary evaluation clone on the first 28 measurable patients there were 8 CR and 11 PR (68%) with an median of time to progression of 10 months

Studies 9301 and 9302: Preliminary data from this two studies were presented at the ASCO meeting this year as a poster in one joint analysis from 235 patients included between 1994 and 1996 (2); 168 breast cancer patients with 10 or more affected axillary lymph nodes after surgery (study 9301:group 1) and 37 locally advanced tumors with 4 or more N+ (group 2) or inflammatory breast cancer (30 patients) with chemo-sensitive disease

after primary chemotherapy (group 3), both from study 9302. Characteristics of patients in-group 1, 2 and 3 were respectively: median age 47, 46 and 45 years old. Median pathological affected lymph nodes 16 (10–12:40%; 13–15:19%; 16–19:21%; >19:20%), 7 (4–9:72%; 9:28%), and 6 (0–3:40%; 4–9:37%; 9:23%). Estrogen receptors were positive in 42%, 59% and 30% respectively in-groups 1, 2 and 3. Histological grade was in-group 1: GI 6%, GII 30%, and GIII 50%, unknown 14%. In group 2: GI 0%, GII 54%, GIII 30%, unknown 16% and in group 3: GI 3%, GII 33%, GIII 17%, unknown 47%. Median follow up was 33 months (19–61), 30 months (19–52) and 30 months (19–52) respectively in each group. Three year disease-free survival (DFS) is 65% (CI 61–69), 90% (CI 84–96) and 43% (CI 33–53). Three year overall survival is 79% (CI 74–84), 94% (CI 89–99) and 81% (CI 73–89). There were 3 treatment-related deaths (1.2%). In comparison with the group historical results achieved with standard adjuvant chemotherapy, HDC with STAMP V and stem cell transplant support may increase DFS and OS in patients with high-risk breast cancer with 10 or more N+ and 4 or more locally advanced tumors after primary chemotherapy. However, it does not provide any advantage in patients with inflammatory breast cancer. New Studies: patients with metastatic breast cancer not candidate for study 9303 or if the center decided to stop the inclusion in that protocol since January 1998 the EBDIS study from Ireland were accepted as SOLTI protocol with number 9703.

The Group decided also to joint the European Study for high-close in Small Cell Lung Cancer and one study for Ovarian Carcinoma was also pending for approval.

For the near future the Group will develop studies in other tumors and areas as the biologic treatment of Breast Cancer and other tumors.

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High dose chemotherapy in the adjuvant setting for high risk breast cancer patients – Results from a randomized study

Jonas Bergh. *On behalf of the SBG 9401 study group; Dept of Oncology, Radiumhemmet, Karolinska Institute & Hospital, Stockholm, Sweden; 27 centres in Denmark, Finland, Sweden*

525 high risk, e.g. ≥8 positive axillary nodes or ≥5 positive nodes and receptor negativity and high S-phase, breast cancer patients were randomised during the study period March 1, 1994 to March 4, 1998, between tailored and dose escalated FEC versus conventional FEC followed by autologous peripheral blood stem cell supported high dose therapy with CTC_b. Patients in both arms received loco-regional radiotherapy followed by tamoxifen at 20 mg/day for 5 years. In order to avoid stage migration we applied very similar staging criteria compared with our previous studies. The inclusion figures have been compared with our population based cancer registries, and we thus conclude our study population to be very representative for this high risk group of patients. All analyses were performed according to the intention to treat principle.

At a median follow-up of 23.7 months we have 66 relapses in the tailored FEC arm and 92 in the high dose arm with CTB_b. This difference is not statistically significant according to the Whitehead model.

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Randomized studies of high-dose chemotherapy in high-risk breast cancer in The Netherlands

S. Rodenhuis[1], E.G.E. De Vries[2]. [1]*Antoni van Leeuwenhoekhuis, Medical Oncology Dept., Amsterdam;* [2]*University Hospital Groningen, Medical Oncology Groningen, Netherlands*

High-dose chemotherapy is frequently employed in the adjuvant treatment of high-risk breast cancer, but its role in this setting has not been established. We have published a randomized study of 81 patients with infraclaviculair node-positive breast cancer, which did not show any survival advantage for high-dose therapy (Rodenhuis S et al, Lancet 1998; 352: 515). Although the morbidity in this study was acceptable and there were no toxic deaths, a previously unreported long-term toxicity was identified: Neuropsychological sequelae were more often seen in the high-dose arm than in the standard arm (Van Dam et al, JNCI 1998; 90: 210). Early results of larger randomized studies are becoming available. The largest randomized study, that of the Netherlands Working Party for High-dose Therapy in Solid Tumors, had randomized 860 patients with 4 or more tumor-positive axillary lymph nodes in April 1999, and will close in June 199, when >880 patients have been accrued. This study has the statistical power to detect a 10% survival advantage for high-dose therapy.

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Review of North American high dose trials

K. Antman[1]. [1]*Columbia University, Division Medical Oncology, New York, United States*

Four North American randomized trials of high dose therapy in high-risk primary and metastatic breast cancer are published in at least abstract form, and two are ongoing.

Adjuvant: The CALGB Intergroup study of Peters et al, compared high vs. intermediate dose CBP after a CAF induction in 783 randomized patients. (Proc ASCO 1999;18:1a) Although low dose CBP is not a standard regimen, scientifically, the design is a pure comparison between high and low dose CBP. This BCNU containing regimen had a 7.4% mortality, which varied with the experience of the transplant center and increased with patient age. With a median of 3.6 years of follow-up, at the time of presentation at ASCO, there was a trend for improved PFS for high dose chemotherapy, but no difference in survival. PFS is at 70% and therefore only 1/3 of the predicted relapses have occurred.

An MD Anderson Hospital study, closed for lack of accrual with 78 patients, showed no advantage for high dose chemotherapy. (Proc ASCO 1998;17:12) Transplant mortality was 1/39 (2.5%)

Metastatic: The Philadelphia Intergroup study, the number of patients randomized is 199, 36% of the 535 patients entered. (Proc ASCO 1999;18:1a) An additional 18% of the randomized patients were ineligible or did not receive their assigned treatment. Responders to 4 to 6 cycles of CAF or CMF chemotherapy were randomized to high dose CTCb versus continued CMF until progression or for up to 2 years. Disease free and overall survival are similar. Mortality on the BMT arm was 1%.

In a Duke CR study, 98 patients who attained a CR were randomized between a BMT immediately vs. at the time of relapse. Disease free survival was significantly improved for the immediate BMT group, but survival favored the group getting delayed BMT. (Proc ASCO 1996;15:121)

Because of the very different designs and follow-ups, any conclusions remain controversial.

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Oesophageal cancer – Who benifits from neoadjuvant therapy

U. Fink[1]. [1]*Klinikum rechts der Isar, Department of Surgery, München, Germany*

Surgery remains the mainstay of therapy in patients with potentially resectable stages with both squamous cell and adenocarcinomas of the esophagus provided a compete resection (R0) can be accomplished. However the vast majority of patients present with locally advanced stages. To increase the rate of complete resections neoadjuvant (preoperative) therapy (chemotherapy [CTx]or simultaneous or sequential radiochemotherapy [RTx/CTx]) have been introduced into the multimodal treatment since more than 20 years. Preoperative CTx, mainly on the basis of cisplatinum/5-FU has shown to be feasible and does not increase the rate of postoperative morbidity or postoperative mortality. However there was no significant increase in the rate of complete resections consistently observed. Preoperative RTx/CTx increases the response rate and inproves local tumour control, but is associated with substantial perioperative morbidity and mortality. Because of these conflicting datas the role of neoadjuvant therapy and the treatment of patients with primary resectable tumour stages remains controversial.

A potential benefit appears to be limited to a subgroup of patients responding either clinically or pathologically to neoadjuvant therapy. On the contrary non responding patients have a disappointing prognosis even after a complete resection. The answer to the question whether patients who respond to neoadjuvant therapy have biologically more favorable tumours than non-responders may be obtained by investigations of molecular markers (e.g. cyclin D1, p53, c-erb-B2, p16 etc.) on pretherapeutic biopsies. Tumour thymidylate synthase (TS) levels appear to be predictive of both response to neoadjuvant therapy and survival. TS expression may help to stratify patients for 5-FU containing neoadjuvant chemotherapy regimens.

However due to tumour cell heterogeinity the predictive value of investigations performed on biopsies may be limited.

Positron emission tomography (PET) offers another method for response prediction. According to our preliminnary results the lack of a decrease in FDG uptake after 2 courses of preoperative CTx (day 15) identifies non responding patients with sufficient probability. Therefore research must focus on modalities with high accuracy that allow pretherapeutic identification of those patients who will or will not respond to neoadjuvant therapy.