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

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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

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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)

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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

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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