mean value increased to 14,10 pg/ml (SD: 14,10) (p=0.007). Moreover, IL-6 decreased to 10,78 pg/ml (SD: 12,38) after 48 hours (p=0.263) and persisted stable (14,97 pg/ml; SD: 14,86) after 1 week (p=0.362). IL-8 levels did not show any statistically significant modification from the basal values after P administration. Statistical analysis showed a significant negative correlation between VEGF values and gamma-IFN values (p= 0.016) and a significant positive correlation between VEGF and IL-8 (p=0.040).

Conclusions: Our data show that P has a powerful antiangiogenic effect mediated by a statistically significant increase in VEGF levels persisting also after one week from the administration of the drug.

974 POSTER DISCUSSION

The expression of vascular endothelial growth factor(VEGF) is a highly significant prognostic factor in stage IB carcinoma of the cervix

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Purpose: The aim of this study was to clarify the role of VEGF expression as an independent prognostic factor and to identify the patients at high risk for poor prognosis in stage IB cervical cancer.

Methods: A total of 118 patients with stage IB cervical cancer who had radical hysterectomy and pelvic lymph node dissection were included in the study. All known high risk factors of the patients were pathologically confirmed from the surgical specimen. Of the 118 patients, 88 patients were treated with postoperative radiotherapy and/or chemotherapy. VEGF expression was examined using immunohistochemistry in formalin-fixed, paraffin-embedded specimens of post-hysterectomy surgical materials. A semiquantitative analysis was made using a scoring system of 0, 1, 2, and 3 for increasing intensity of stain. We classified the patients with scores from 0 to 2 as low staining intensity and the patients with a score of 3 as high staining intensity.

Results: Of the 118 patients, 35 patients (30%) showed high staining intensity (3) of VEGF. Strong correlations were found between the high staining intensity of VEGF and both deep stromal invasion (p=0.009) and the positive pelvic node (p=0.024). The 5-year overall and disease-free survival rates for all 118 patients were 94.6% and 92%. The 5-year overall (p=0.01) and disease-free survival (p=0.0014) rates were 97.1% and 98.6% for low intensity (0, 1, and 2) of VEGF and 90.7% and 81.7% for high intensity of VEGF, respectively. Pelvic and distant failures for low versus high intensity of VEGF were 1.2% versus 17.1%, (p=0.003) and 0% versus 14.3% (p=0.002), respectively. In a Cox multivariate analysis of survival, the high staining intensity of VEGF (p=0.008) and the positive pelvic node (p=0.013) were significant prognostic factors for overall survival. The high staining intensity of VEGF (p=0.013), vascular invasion (p=0.02), and bulky mass (p=0.034) demonstrated as significant prognostic indicators for disease free survival.

Conclusion: These results showed that the intensity of VEGF expression was a highly significant predictor for pelvic and distant failure and the most significant prognostic factor of overall and disease free survival for the patients with stage IB cervix cancer treated with radical surgery. We strongly suggest that the immunohistochemistry for VEGF expression be performed in a routine clinical setting in order to identify patients at high risk for poor prognosis in cervical cancer.

975 POSTER DISCUSSION

Inhibition of neuroblastoma-induced angiogenesis by fenretinide

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Purpose: Retinoids partecipate in the control of cell proliferation, differentiation and foetal development. The synthetic retinoid fenretinide (HPR) inhibits carcinogenesis in various animal models and it has been suggested that retinoids are effective inhibitors of angiogenesis.

Methods: The effects of HPR on certain endothelial cell (EC) functions were investigated in vitro, and in vivo, by using the chorioallantoic membrane (CAM) assay.

Results: HPR inhibited VEGF- and FGF-2-induced EC proliferation without affecting endothelial motility; moreover, it inhibited growth factors-induced angiogenesis in the CAM assay. A significant anti-angiogenic potential of HPR has been observed also in neuroblastoma (NB) biopsies induced angiogenesis in vivo. We previously demonstrated that supernatants derived from NB cell lines stimulated EC proliferation. Here, we show that this effect is abolished when NB cells were incubated in the presence of HPR. VEGF- and FGF-2 specific ELISA assays, performed on both NB-cells derived conditioned medium and cellular extracts, indicated no effect of HPR on the level of these angiogenic cytokines. Moreover, RT-PCR analysis of VEGF and FGF-2 gene expression confirmed the above lack of effect. HPR was also able to significantly repress the spontaneous growth of EC, requiring at least 48-72 h of treatment with HPR, following by a progressive accumulation of cells in G1 at subsequent time points. Finally, immunohistochemistry experiments performed in the CAM assay demonstrated that endothelial staining of both VEGF receptor-2 and FGF-2 receptor-2 was reduced after implantation of HPR-loaded sponges, as compared to control CAM's.

Conclusion: These data suggest that HPR exerts its antiangiogenic activity through both a direct effect on EC proliferative activity and an inhibitory effect on the responsivity of the EC to the proliferative stimuli mediated by angiogenic growth factors.

976 POSTER DISCUSSION

Pancreatic tumor growth is regulated by the balance of positive and negative modulators of angiogenesis

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There is increasing evidence for the implication of tumor-derived angiogenic and anti-angiogenic factors in tumor growth in vivo. In this study we examined how changes in the balance between these factors regulate the growth of a tumor in a pancreatic cancer model in vivo. The pancreatic cancer cell line Hs-776T (HS-W) displays slow growing tumors and we have isolated a natural occurring variant (HS-R), which grew tumors more rapidly. In vitro, HS-W and HS-R produce low amounts of vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF) but only HS-W cells produce endostatin. In order to examine the effect of over-expression of angiogenic factors on pancreatic tumor growth in vivo, we have transfected HS-W cells with human VEGF165 cDNA. Upon injection of VEGF overexpressing cells into immune deficient mice, rapidly growing tumors were observed. In contrast, mock transfected cells, HS-PCP, formed small tumors similar to parental cells. Tumors of VEGF-transfected clones were highly vascularized with many dilated blood vessels, lined by a single layer of CD31-positive endothelial cells. PCNA staining showed high proliferation index in VEGF producing tumors and conversely, apoptosis, as determined by TUNEL staining, was higher in HS-W, moderate in HS-R and low in VEGF producing tumors. Collectively, our study confirms that tumor growth is dependent on its ability to increase the angiogenic stimulus or to reduce the amounts of endogenous antiangiogenic factors.

977 POSTER DISCUSSION

Increased angiogenesis in bone metastases of patients with metastatic breast cancer

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Introduction: In a great proportion of patients with metastatic breast cancer, the disease metastasizes to the bone causing pain, hemopoietic insufficiency and a reduction in the quality of life. However, the mechanisms that contribute to bone metastasis are poorly understood. Therefore, the aim of this study is to clarify the mechanisms of tumor-endothelial-cell-interaction and to evaluate the role of angiogenesis for the development of bone metastases in patients with breast cancer.

Methods: Specimens from patients with metastatic breast cancer and non-malignant bone tissue were studied. Paraffin embedded sections were stained with hematoxylin and eosin and examined for the presence or absence of malignant tissue. Furthermore, an indirect immunoperoxidase staining with an monoclonal antibody against the CD31 epitope was used to identify vascular endothelium. Microvessel density (MVD) was counted in hot spots as well as in representative areas of the adherent section.

Results: To date 27 bone metastases and 26 non-malignant bone tissue specimens have been examined. The number of microvessels in bone

metastases from patients with breast cancer is significantly increased comparing to the MVD in non-malignant bone tissue when areas of low, medium and highest vascular density were examined (1,8 ±0,71 versus 24,12 ±1,97). Not surprisingly, this difference is even greater, when only hot spots are evaluated.

Conclusions: There is now for the first time evidence of increased microvessel density in bone metastases of patients with breast cancer, which supports the hypothesis of an important role of angiogenesis in bone metastasis. Furthermore, this study suggests, that an antiangiogenic therapy might be an efficacious treatment. Further studies, clarifying the role of angiogenic factors and their receptors in bone metastasis are underway.

Supportive care & quality of life

978 POSTER DISCUSSION

Use and complications of subcutaneous infusion ports. A retrospective study to identify risk factors

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Subcutaneous infusion ports have become important tools in oncological patient care and its use has become standard procedure for long term venous acces. However different complications may arise with its use. The identification of different risk factors may help to reduce their incidence.

We performed a retrospective study on 437 patients, followed at the department of medical oncology and haematology of our institution, in whom an infusion port was inserted between October 1993 and October 1998. All complications were recorded and and a statistical analysis was performed to look for possible predisposing factors.

The main complications were thrombosis (8.46%) and catheter dysfunction (4.86%). Pocket infection and catheter related bacteremia occurred in 4.36% of the cases. Rare complications were: port rotation, catheter disconnection, catheter rupture or kinking, and extravasation.

There was a strong correlation between the anatomical position of the catheter and the incidene of thrombosis and dysfunction. Of those patients in whom the catheter tip was located in the brachiocephalic vein, 45% experienced a thrombotic complication ($p<0.001$). Patients in whom the catheter tip was located in the upper third part of the superior caval vein had thrombosis in 19% of cases ($p<0.01$). In this latter group, port dysfunction rate was 16.7% ($p<0.01$).

This study emphasizes the importance of careful catheter tip positioning in patients with a subcutaneous infusion port. Tightened guidelines and rigorous radiological control after insertion are warranted. A classification in different risk groups according to radiological criteria was proposed. It might serve to select high-risk patients, who could benefit from a prophylactic antithrombotic treatment.

979 POSTER DISCUSSION

Quality of life influenced by primary surgical treatment for stage I-III breast cancer - long-term follow-up of a matched-pair analysis

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Breast conserving therapy has been demonstrated to be just as safe and a less disruptive experience compared to mastectomy for surgically manageable breast cancer. There is, however, no agreement in the literature about the impact of these procedures on several important aspects of quality of life (QoL). The purpose of the present study is to compare the long-term impact of these two surgical approaches on Qol in patients with identical tumor stages and to suggest possible shortcomings of the standard QoL questionnaires.

Between August 1999 and May 2000, QoL questionnaires were answered by 152 pair-matched patients at the I. Frauenklinik, Ludwig-Maximilians University Munich, as part of routine follow-up examinations. The pairs of patients, each consisting of one patient after mastectomy and one after breast conservation, were selected according to the highest degree of equivalence in tumor stage. All patients had been initially treated for stage I-III breast cancer without evidence of distant metastases. The QoL was evaluated by using the QLQ-C30 questionnaire version 2.0 of the EORTC Study Group on Quality of Life. We formulated seven additional questions about the patients' satisfaction with the primary surgical treatment modality as viewed from their current perspective. The QoL questionnaires were answered after a median interval of 46 months following primary treatment.

Tumor stage, prognostic factors, and adjuvant systemic treatment were well balanced between the two groups. No differences between the two groups were observed in terms of all QoL items measured by the QLQ-C30. Our additional questions, however, revealed that patients in the mastectomy group were less satisfied with the cosmetic result of their primary operation ($P< 0.0001$), were more likely to feel basic changes in their appearance ($P< 0.0001$), and were more likely to be emotionally stressed by these facts ($P< 0.0001$). From their perspective at the time of completing the questionnaires, 11 patients in the mastectomy group (15%) would decide differently about the surgical treatment modality, compared to only 3 patients (4%) in the breast conservation group ($P=.025$).

While the primary surgical treatment modality seems to have no long-term impact on the general QoL, certain body image related problems may be caused by mastectomy. Standard measuring instruments for QoL may fail to detect differences in satisfaction and adaptation with the primary surgical treatment modality.

980 POSTER DISCUSSION

Early intervention with epoetin alfa treats anaemia and improves quality of life in ovarian cancer patients undergoing chemotherapy

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Purpose: Anaemia occurs in up to 60% of ovarian cancer patients treated with platinum-based chemotherapy (CT). This randomised, multicentre study investigated the effect of early intervention (haemoglobin (Hb) level: 10-12g/dL) with epoetin alfa during CT to treat and prevent anaemia.

Patients and Methods: 182 patients were randomised 2:1 to receive 10,000 IU epoetin alfa (EPREX/ERYPO, Ortho Biotech/Janssen Cilag) thrice weekly or best standard of care (BST). Patients had confirmed ovarian cancer and a Hb level of ≃12.0g/dL (mean ±SD: 10.69±0.91g/dL). Patients were assessed at six time points during chemotherapy (baseline; 4-6, 8-9, 12, 16-18 and up to 28 weeks) for Hb, Quality of Life (QoL; Functional Assessment of Cancer Treatment - Anaemia (FACT-An), Cancer Linear Analogue Scale (CLAS) and blood transfusion requirements.

Results: Results are presented on 160 patients (mean age±sd: 59.4±11.6 years). At baseline, the groups were balanced for demographic, treatment and disease-related variables (mean Hb±sd: 10.72±0.94g/dL vs 10.63±0.85g/dl, EPO vs BST). Changes in Hb from baseline were significantly greater in the epoetin alfa group than in the BST group at all time points ($p<0.001$). The differences between groups were most marked at 8-9 and 12 weeks (mean±sd: 2.03±1.45g/dl and 2.01±1.15g/dL, respectively). At 12 weeks, 74% of epoetin alfa patients and 11% of BST patients had achieved Hb values >12.0g/dL. Significantly more BST patients required blood transfusions than did those treated with epoetin alfa (16.7% vs 5.7%, $p=0.041$). A within-group analysis of EPO-treated patients showed significant improvements ($p<0.001$) in QoL scores (CLAS: energy, activities and overall QoL) during CT; the average score of all three scales increased by 29% between baseline (55.33±23.13) and last observation (71.32±24.53), with increases of up to 37% seen at 12 weeks. No significant improvements were observed in the BST patients. More detailed analysis, including an across-group comparison of QoL is ongoing.

Conclusions: Early treatment (Hb: 10-12g/dL) with epoetin alfa of ovarian cancer patients undergoing CT significantly increased Hb levels. Hb levels were maintained up to 2g/dL higher in patients receiving epoetin alfa than in those given best standard of care, which reduced the risk of anaemia. Higher Hb levels resulted in fewer blood transfusions and meaningful improvements in QoL.

981 POSTER DISCUSSION

A phase III, double-blind, placebo-controlled, randomized study of novel erythropoiesis stimulating protein (NESP) in patients undergoing platinum-treatment for lung cancer

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Purpose: NESP binds to the erythropoietin (EPO) receptor and stimu-