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'Invading edge vs. inner' vascularisation: Angio-genic and angio-preserving activity in non-small cell lung cancer (NSCLC)

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Purpose: Neo-angiogenesis during neoplastic growth involves endothelial mitogenic and migration stimuli produced by cancer or tumour stromal cells. Although this active angiogenesis takes place in the tumour periphery, the process of vessel remodeling in inner areas and its clinical role remains largely unexplored.

Methods: In the present study we examined comparatively the microvessel score (MS) in the invading edge and in inner areas, in a series of 178 pts with operable NSCLC.

Results: We distinguished three different patterns of vascular growth: *i.* the *type 1*, where low MS was observed in both peripheral and inner tumour areas, *ii.* the *type 2*, where high MS was note in the invading front but low in inner areas and, *iii.* the *type 3*, where both peripheral and inner tumour areas had a high MS. VEGF expresion was associated with type 3 while TP expression was associated with type 2 vascularisation, showing that, although both factors are angiogenic, VEGF (and not TP) substantially contributes to the preservation of the inner vasculature. Both type 2 and 3 cases showed an increased incidence of node metastasis but, type 3 cases had a poorer prognosis even in the N1-stage group.

Conclusion: The present study suggests that angio-genic and angio-preserving tumour abilities are not identical and are controlled by different vasculature related factors. Quantification of these two parameters is feasible by comparatively evaluating the MS in the invading edge and inner areas.

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Tumour angiogenesis and response in combined modality treatment of head and neck cancer

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Purpose: Immunohistochemical examination of biopsies of head and neck cancers were examined with regard microvessel density.

Patients and Methods: From 1984 to 1990 a total of 80 patients were treated by preoperative combined modalities. Patients had histologically verified squamous cell cancer of the oral cavity or oropharynx. Treatment consisted of 50 Gy/25 fractions/4–5 weeks with administration of chemotherapy during the first 5 days of radiotherapy (Mitomycin C on day 1:15 mg/sqm IV bolus, days 1–5: 750 mg/sqm/24 hours by IV infusion for 120 hours). After 4–6 weeks surgery was performed. After preoperative combined therapy the rate of complete response (CR) was 45% (histologically conifrmed by operation). Response rates following radio-chemotherapy was stage dependent: 73% CR in T2, 46% in T3 and 19% in T4, respectively.

We investigated pretherapeutic tumour biopsies from the above preoperatively treated patients with regard to angiogenesis.

Measurement of tumour angiogenesis was performed using the mAb JC (CD31). At low power, areas with the most dense vascularits were determined and the number of microvessels (MVD) were counted at X400 magnification.

Results: Tumour vessel density (MVD-Tu: range 4–33, mean 15) was not significantly different in the tumour stages. Normal tissue vessel density ranged between 6 and 48 (mean MVD-Nt: 20). Patients achieving a CR to preoperative therapy had a higher degree og MVD-Tu than those who responded partially (PR) (16 vs. 14; $p = 0.13$). In 78% of cases the MVD-Nt > MVD-Tu. In these cases the CR was 39% vs. 75% in cases where MVD-Nt < MVD-Tu ($P < 0.05$).

Conclusion: We conlude that measurement of angiogenesis has potential value as predictive factor in radio-chemotherapy in head and neck cancer.

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The importance of timing in thermochemotherapy with tubulin inhibitors

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Purpose: Tumor vasculature has been proposed as a central target in the therapy of solid tumors. Several cytotoxic agents affects tumor blood flow, and tubulin inhibitors like vinblastine and combretastatin A-4 (CA-4) seem particularly effective in reducing tumor perfusion.

Methods: We used laser Doppler flowmetry for continous measurements of tumor blood flow in the s.c. BT4An rat glioma after injection of either vinblastine or CA-4. Guided by these measurements we conducted tumor response studies in which we compared different time-intervals between the administration of drug (vinblastine 3 mg/kg i.v. or CA-4 50 mg/kg i.p.) and tumor hyperthermia (HT; waterbath 44 de.C for 60 min).

Results: We demonstrated that both vinblastine and CA-4 induce considerable time-dependent reductions in tumor blood flow, reaching nadir about 110 min after injection of the drugs. These flow reductions were achieved at well tolerated drug-doses. Injecting vinblastine or CA-4 three hours prior to HT improved tumor response significantly compared to simultaneous administration of the two treatment modalities. The improved tumor response was observed secondary to increased vascular destruction and necrosis in the tumors. Interestingly neither vinblastine nor CA-4 had any significant effect on tumor growth alone.

Conclusion: The tubulin inhibitors vinblastine and CA-4 temporally sensitized tumor vasculature for heating and optimized tumor response could be obtained if timing was adequate.

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Serum erythropoietin level in anemic cancer patients

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Introduction: Anemia, one of the most frequent complications of cancer, is a major concern in cancer patients. Whether it is cancer related or chemotherapy induced, anemia in these patients, in general, cause constitutional symptoms affecting all the daily activities of the cancer patients. Recombinant human erythropoietin (epo) administration replaced blood transfusion in the elective treatment of anemia in cancer patients. Serum epo level, in this regard, is a major reference point in introducing this treatment modality in the supportive care of these patients.

Materials and Methods: We studied serum epo levels in 74 patients with solid tumors and in a control group consisting of 20 otherwise healthy indiviuals without any malignancy, who have only iron deficiency anemia. Serum epo levels were measured by enzyme immunoassay, in cancer patients, without anemia ($n = 34$), in anemic cancer patients ($n = 40$); currently receiving chemotherapy ($n = 21$) or not ($n = 19$). Patients who had chemotherapy induced anemia were further categorized on the basis of whether ($n = 11$) or not ($n = 11$) they had been treated with a CDDP containing regimen. Student t-test was used for the analysis of the results.

Results: Anemic cancer patients were found to have decreased response of erythropoietin for a given hemoglobin level (mean epo 40.1 + 34.7 u/ml), compared with the patients having only iron deficiency anemia (mean epo 69.7 + 68.6 u/ml) ($p < 0.05$). In nonmalignant patients with iron deficiency anemia, erythropoietin response was remarkably high and inversely correlated with the level of hemoglobin level ($r = -0.69$; $p = 0.05$). Although there was no correlation between hb and erythropoietin response in cancer anemia ($r = -0.07$), serum levels of epo were found to be higher in anemic cancer patients (mean epo 40.1 + 34.7 u/ml), compared with cancer patients with normal hemoglobin values (mean epo 19.96 + 18.4 u/ml). There were not any significant difference between epo levels of anemic cancer patients, receiving chemotherapy or not (mean epo 43.7 + 37.7 u/ml and 41.9 + 30.08 u/ml respectively; $p > 0.05$). No difference in serum epo levels were noted in patients treated with CDDP or non-CDDP containing regimens (mean epo 48.36 + 33.12 u/ml and 38.55 + 43.52 u/ml, respectively; $p > 0.05$).

Conclusion: In our study, it was demonstrated that anemia in cancer patients was caused by blunted epo response, rather than its quantitative deficiency. This provides new insights in the supportive care of cancer patients.