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Combination chemotherapy (CT) and secondary resection (SR) results in germ cell testicular cancer (TT)

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Purpose: The aim is assessing results of CT and SR in TT pts, treated at the Oncol Inst Cluj, between 1/82–9/96.

Methods: 203 untreated TT (pts), had 3 [2–6] CT cycles (VAB6 133, BEP 46, EP 26), after orchidectomy. In partial responders (PR) with negative markers (mk–) a SR was done.

Results: *Characteristics.* age 30 [14...53]; st I 31, IIA 30, IIB 69, III 73 pts; histology (H): seminoma 40, nonseminomatous 125, mixed 38. Risk group (Indianapolis): high (HR) 57; intermediate (IR) 54, low (LR) 92 pts. *Toxicity:* 1 toxic death (acute renal failure). *Response:* There were 151 objective responses (OR) in 172 st. II–IV pts. (88%, CI 83%–93%), with 98 (57%) CR. *Post CT surgery:* 29 PR (Mk–) (Indiana LR 6, IR & HR 23) underwent SR (retroperitoneal tumour 28 pts, pulmonary 1 pt). Complete SR was possible in 16 pts (55%). H findings: necrosis 14 (48%), active tumour (AT) 11 (38%), teratoma 4 pts (14%). AT was not found in LR pts, and was more frequent after VAB6 than BEP&EP (88% vs 25%, $p < 0.01$). Initial H and dimension of the residual mass after CT did not influence H findings at SR. *Survival* (S): With a follow-up of 60 m [6+...144+], 5 y overall S was 67%. Prognostic factors for S ($p < 0.01$) in univariate analysis were: weight loss (<5% vs ≥5%: 76% vs 14%), performance status (0–1 vs 2–4: 81% vs 31%), stage (I vs IIA vs IIB vs III: 90% vs 96% vs 64% vs 46%), Indianapolis LR vs pooled IR & HR: 43% vs 91%), obtention of a CR (CR vs others: 89% vs 26%), CT protocol (BEP&EP vs VAB6: 95% vs 61%). S was not influenced by the initial H type, the postorchydectomy value of AFP, HCG, LDH. For SR pts, S for totally resected vs unresectable was 100% vs 26% ($p < 0.01$). As of Sept 1996, 158 pts are alive (112 CR, 28 PR) and 45 have died: 43 pts disease progression (7 locoregional, 11 metastases only, 25 pts both), 1 pt acute renal failure, 1 pt other disease.

Conclusions: 1). Our results confirm the superiority of Etoposide containing regimens over older VAB6, in terms of improved survival and less frequent active tumour in SR specimens. 2) In our series, there was no difference in S between Indianapolis IR and HR categories, but distinction between this mixed group and LR pts remained predictive for the individual outcome.

Angiogenesis and tumour markers

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Combretastatin A-4, an agent that displays selective toxicity towards tumour vasculature

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Purpose: The study was designed to evaluate and characterise the antivascular effects of the tubulin binding agent combretastatin A-4 and its soluble prodrug, both *in vitro* and *in vivo*.

Methods: The cytotoxic effects of the drugs were examined *in vitro* by a viable cell quantitative assay. *In vivo*, the extent of vascular mediated haemorrhagic necrosis was assessed histologically.

Results: The drug display potent effects toward tumour associated and proliferating endothelium, when assessed *in vitro*. Quiescent endothelium is quite resistant to the effects of these agents. Selective vascular shutdown, within experimental human breast cancer models *in vivo*, was obtained following the systemic administration of combretastatin A-4 prodrug at 100 $mg \cdot kg^{-1}$.

Conclusion: These studies have identified combretastatin A-4 and its soluble prodrug as agents that can elicit selective effects against proliferating endothelial cells in vitro, with a rapid and extreme vascular shutdown within tumours *in vivo*, at doses <10% of the MTD.

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Homeobox genes expression in endothelial cells and their potential role in angiogenesis

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Purpose: Angiogenesis, is a complex biological process that plays a determining role during physiological events and in pathological phenomena including cancer. Because the genesis of a blood vessel is a complex morphogenic event, it is likely that the genetic program activated during angiogenesis is under the control of one or several master gene(s). In our study, we have tested the hypothesis that angiogenesis could be controlled by specific expression of a panel of homeobox (HOX) genes. In humans, 39 HOX genes have been identified. While the exact function of most HOX genes remain to be established, there is now a body of experimental evidence suggesting that they are involved in the control of normal development and in regulation of gene expression in cell differentiation.

Methods: Using reverse transcriptase-polymerase chain reaction technique (RT-PCR) and RNAse protection assays with specific riboprobes we analyzed the expression pattern of the HOXB gene cluster in human umbilical vein endothelial cells (HUVEC).

Results: Amplification of cDNA fragments synthesized from HUVEC RNA led to the identification of four HOX genes expressed in human umbilical vein endothelial cells: HOX B1, B4, B8 and B9. RNAse protection assays enabled already to confirm the expression of HOX B4, B8 and B9 genes.

Conclusion: Our study is the first demonstration of HOX genes expression in endothelial cells. Our future work will attempt to elucidate the role of these coordinator genes in the control of angiogenesis.

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A high pretreatment serum level of VEGF is associated with poor outcome in small cell lung cancer

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Purpose: Vascular endothelial growth factor (VEGF) is an important regulator of angiogenesis, an endothelial-cell specific mitogen and a vascular permeability factor. The clinical significance of serum VEGF (S-VEGF) is unsettled.

Methods: We measured pretreatment S-VEGF concentrations by ELISA from sera of 68 untreated patients with small cell lung cancer (SCLC) and compared the results to clinical parameters. The patients were treated with 6 cycles of cisplatin and etoposide, and were randomized into 3 arms to receive recombinant interferon, leukocyte interferon or neither.

Results: S-VEGF concentrations ranged from 70 to 1,738 pg/ml (mean, 527 pg/ml). The patients with a PR or CR had lower pretreatment S-VEGF levels than those with an NC or PD ($P = 0.0083$). A high (>527 pg/ml) S-VEGF level was associated with poor survival ($P = 0.012$), and all 3-yr survivors had lower than the mean S-VEGF at diagnosis. In a multivariate analysis S-VEGF had independent prognostic value together with stage, and the estimated 3-yr survival of the patients with limited stage and a low S-VEGF was 41% (25% of all patients, $P = 0.0055$).

Conclusion: A high pretreatment S-VEGF level is associated with poor response to treatment and unfavourable survival in patients with SCLC treated with combination chemotherapy.

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Focal expression of platelet-derived endothelial cell growth factor (PD-ECGF) triggers local neo-angiogenesis in non-small cell lung cancer

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Purpose: Platelet-derived endothelial cell growth factor (PD-ECGF) or thymidine phosphorylase has been proved to have considerable in vitro angiogenic activity. We immunohistochemically evaluated possible correlation of PD-ECGF overexpression with angiogenesis in non-small cell lung cancer (NSCLC).