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INHIBITION OF BCL-2 BY ANTISENSE OLIGONUCLEOTIDES REDUCES TUMOR SIZE AND REDUCES CHEMOTESTISTANCE OF HUMAN MELANOMA IN SCID MICE

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Malignant melanoma, a prime example for poor response to various treatment modalities including chemotherapy, expresses bcl-2 in up to 90 % of all cases. The anti-apoptosis gene bcl-2 belongs to a new category of oncogenes capable of regulating programmed cell death. Induction of programmed cell death has been proposed recently as the mechanism of action for a variety of chemotherapeutic agents. In the present study we could show a sequence specific downregulation of bcl-2 protein by phosphorothioate antisense oligonucleotides in human melanoma under *in vitro* conditions. In addition, we established a SCID-hu xenotransplantation melanoma model and evaluated the role of bcl-2 in the biology and chemoresistance of human melanoma *in vivo* by using the same antisense approach. We could demonstrate that antisense induced downregulation of the bcl-2 gene product of human melanoma grown in SCID mice results in a statistically significant decrease in tumor weight. Bcl-2 antisense treatment also reduced the chemoresistance of human melanoma rendering animals without detectable tumors after a combined bcl-2 antisense-dacarbazine treatment. Reverse controls and mismatch phosphorothioate oligonucleotides had no such effects. These results strongly suggest an antisense mode of action, but this has yet to be confirmed at the RNA level. Our findings stress the notion that downregulation of bcl-2 in human melanoma may be a novel approach to overcome chemoresistance in this type of malignancy.

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TREATMENT, RESULT AND FOLLOW-UP OF JAW,S SARCOMAS

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We have examined 149 patients with sarcomas of the jaws: 86 cases with upper jaw tumors and 63 cases with low ones. The most common tumors were osteogenic sarcoma (22,1%), chondrosarcoma (21,5%) and malignant Fibrous histiocytoma (9,4%). The most jaw,s sarcomas (79,8%) involved the surrounding tissues and organs. The main method of treatment was surgical or combined therapy, that were performed at 117 patients.

5-years survival rate was 49%. 11 patients with radiosensitive tumors were treated by radiation and chemotherapy with 50% 5-year survival rate. The main differences of clinical behaviour jaw,s sarcomas are: rate distant metastases - 18 cases (12,1%), and frequent recurrences - 54 cases (46,2%).

Surgical treatment is a method of choice of recurrences of jaw,s sarcomas with 49% 5-year survival rate. The most important prognostic factor is local spread of tumor: 55,7% and 64,2% 5-year survival rate for localized upper and low jaw,s sarcomas respectively and 26,7% and 25,2% for advanced ones. We applied some complex methods of reconstructive surgery.

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MEASUREMENT OF STRESS DIMENSION IN CANCER PATIENTS

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According to the concept of stress dimension (G.W.Albee, 1981) 112 cancer patients were examined using psychometric questionnaire. Cancer stress dimension (CSD) was calculated using the formula:

$$CSD = \frac{O + S}{A + P + C}$$

O - objective estimation of the stressor (disease stage, performance status, etc.);

S - subjective estimation of the stressor (fear, menace etc.);

A - assistance factor (family, religion, friends, books, group counselling etc.);

P - personality factor (belief in cure);

C - competence factor (ability to cope).

Each field of stress dimension was covered by 3 - 5 specific items ranged from 1 to 5. The score of the numerator and denominator have been transformed to lie between 0-100.

Stress dimension varied from 0,6 to 2,5.

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Management of Clinically Positive Axillary or Inguinal Lymph Nodes in Patients with Malignant Melanoma -A Decision Analysis

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Background: Currently no consensus exists concerning the management of melanoma patients with palpably positive axillary or inguinal lymph nodes. Some authors recommend immediate lymph node dissection whenever regional lymph nodes are palpably positive, others additionally recommend follow up by sonography or fine needle aspiration (FNA) to evaluate the clinical findings.

Objective: The objective of this research was to determine the utility of different management strategies for these patients.

Methods: Decision analysis was used to evaluate a utility value, which represents the appropriateness of the given outcomes of four management strategies for the diagnostic workup and treatment of melanoma patients with palpably positive axillary or inguinal lymph nodes: (1) lymph node dissection (2) lymph node sonography (3) a sequence of lymph node sonography and FNA and (4) FNA.

To calculate path probabilities, the required data were obtained from the literature. Sensitivity analyses were performed on all key variables.

Results: At our baseline estimates, lymph node sonography followed by FNA in case of ambiguous sonographic findings was superior to the other management strategies. Fixing all other variables at their baseline, sensitivity analysis revealed that if the prevalence of metastatic disease given positive palpable findings exceeds 97% the immediate dissection of lymph nodes without performing further tests would be the most favourable strategy.

Conclusion: From the perspective of appropriateness of diagnosis and treatment, sonography followed by FNA in case of ambiguous sonographic findings is the most preferable management strategy of melanoma patients with clinically positive axillary or inguinal lymph nodes.

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INDUCTION OF IMMUNOMEDIATED DISEASES BY RECOMBINANT HUMAN GRANULOCYTE-MACROPHAGE COLONY-STIMULATING FACTOR DURING CANCER TREATMENT

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Recombinant human granulocyte-macrophage colony stimulating factor (rh GM-CSF) is widely used in the treatment or prevention of neutropenia induced by cytostatic regimens. Recent studies with this cytokine have shown several local and/or systemic side effects. We herein report on four patients with different tumor entities receiving rh GM-CSF as a part of their intensified cytostatic regimen. All patients described above developed immune phenomena (sicca-syndrome, arthralgia, hyperthyroidism, and pneumonitis, respectively) during or following subcutaneous treatment with rh GM-CSF. Pathological changes in immunological serum parameters as well as histopathological findings accompanied the clinical symptoms. Our findings suggest that the therapeutic application of rh GM-CSF should be monitored carefully in order to avoid the development of immunologic diseases. Otherwise, patients surviving their malignant disorder might thereafter suffer from autoimmune diseases triggered by GM-CSF.

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A PROSPECTIVE RANDOMIZED TRIAL ON NEOADJUVANT AND ADJUVANT CHEMO- AND RADIOTHERAPY IN PRIMARILY INOPERABLE SOFT TISSUE SARCOMA

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Advanced soft tissue sarcoma constitutes a major therapeutic problem. In the current study 22 patients with soft tissue sarcoma inoperable by limb sparing techniques with or without distant metastases received 8 cycles of chemotherapy consisting of ifosfamide, adriablastin and DTIC (IFADIC) in intervals of 14 days made possible by the application of G-CSF on days 4-13 of each cycle. 4 applications of IFADIC were given preoperatively, whereas the other 4 were administered following surgery. The patients were randomized to receive radiotherapy (51 Gy, hyperfractionated) either preoperatively (during chemotherapy cycles 2 and 3) or postoperatively (during chemotherapy cycles 6 and 7). During radiotherapy the simultaneous application of adriablastin was avoided, resulting in the sole administration of ifosfamide and DTIC (IFDIC).

During a mean observation period of 18±7 months (recruitment of patients started in November 1992 and is reported until December 1995), 3 patients in the group receiving preoperative radiotherapy and 3 patients in the group with postoperative radiotherapy are in complete remission. In the group with preoperative radiotherapy (11 patients), 4 patients are in progressive disease, out of which 3 have died. In the postoperative radiotherapy group (11 patients), 5 patients are experiencing progressive disease, out of which 3 have died from metastatic soft tissue sarcoma (11 patients). At the current time the rest of the patients is in progress and cannot be evaluated. Although due to the low number of patients with this rare disorder no difference was detected in the course of their disease in relation to the application of pre- versus postoperative radiotherapy, this therapeutic approach with the primary aim of curing the patients from their disease was successful, in that 6 patients out of 16 are free of disease and have received limb-sparing surgery. 1 patient is a partial responder, whereas 9 patients have experienced progressive disease. At present, 6 more patients are in progress. We thus believe that at the current time this approach of combined augmented chemo- and radiotherapy leads to complete remission and makes limb-sparing surgery possible in a considerable proportion of patients with primarily inoperable soft tissue sarcoma.