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IN VITRO EVALUATION OF BIOLOGICAL ACTIVITY OF SYNTHETIC THYMOPENTIN /Tp5/ AND ITS ANALOGS HUMAN /HSp5/ AND BOVINE SPLENOPENTINS /BSp5/

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Biological activity of synthetic Tp5 and its analogs HSp5 and BSp5 were studied in vitro on mouse and human lymphoid cells as well as on human leukemia cell lines K-562 and CEM. Incubation of mouse thymocytes and splenocytes with Tp5, HSp5 and BSp5 resulted in some enhancing of DNA synthesis. HSp5 and BSp5 stimulated preferably splenocytes.Preincubation of human peripheral blood lymphocytes with Tp5, HSp5 and BSp5 and after that stimulated with mitogen PHA, resulted in significant increasing of lymphocyte proliferation when stimulated with suboptimal doses of PHA. HSp5 and BSp5 were more active then Tp5. The percentage of E-RFC did not change after treatment with Tp5 and its analogs. Tp5, HSp5 and BSp5 did not stimulate proliferation of K-562 and CEM leukemia cells.

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TREATMENT OF POOR-PROGNOSIS HEAD AND NECK CANCER (HNC) WITH ALPHA-INTERFERON (α-IFN) AND CONCOMITANT RADIOTHERAPY.

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α-IFN has sensitizing properties, when used in combination with RT. Fourteen patients with T4N3, recurrent or metastatic HNC were treated with recombinant α-IFN and RT. Two levels of doses, 1.5×10^6 IU/m²/day and 2×10^6 /m²/day were administered subcutaneously to 8 and 6 patients, respectively, on a 3 day-a-week schedule for 8 weeks, concurrently to conventional RT (total dose 58-70 Gy). Additional 8 patients received RT alone were considered as control group. Toxicities mainly consisted of transaminases and alkaline phosphatase serum levels increasement. No significative differences in toxicity were noted between the two dose levels. Overall response rate was 88% (12/14) with 5 CR. The results of the present study indicate that the combined α-IFN and radiotherapeutic approach is feasible in the clinical setting.

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SPONTANEOUS VARIATIONS OF IFN-g AND RIL-2 SERA CONCENTRATIONS, DURING 8 HOURS IN ADVANCED MALIGNANT MELANOMA CANCER PATIENTS.

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In malignant melanoma patients, we have performed a research of prognostic factors. We have observed a great dispertion in sera concentrations of RIL-2 (Interleukin 2 Receptor) (Range: 20.36 to 41.66 picog/ml) and IFN-g (Interferon gamma) (Range : 11.73 to 26 picog/ml). We used the ELISA method. In order to explain this variation, we have evaluated in six patients sera concentrations each 20 minutes during 8 hours, in the same day period and without concomitant treatment or medication. We have observed variations of 51.12% for RIL-2 and 54.8% for IFN-g. Spectral analysis (Algorithm of COOLEY and TUKEY, better known as FAST FOURIER TRANSFORM) of these results shows a periodic variation of RIL-2 and IFN-g sera concentrations. These cytokines grow up in sera each 45 and 120 minutes.

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A PHASE II STUDY OF CONTINUOUS INTRAVENOUS INFUSION (CIVI) RECOMBINANT IL-2 AND SUBCUTANEOUS α-INTERFERON BY SEQUENTIAL ADMINISTRATION IN ADVANCED RENAL CELL CANCER

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Recombinant interleukin-2 (rIL-2) and α-interferon (IFN) are both active in renal cell cancer (RCC), but their concurrent administration could result in additional toxicity. Preclinical evidence of synergistic activity of the two drugs given sequentially is founded on the enhanced expression of MHC-I-class antigens on tumor cell surface induced by α-IFN with increase of IL-2-mediated cytotoxicity. A phase II study of CIVI rIL-2 followed by subcutaneous α-IFN has been carried out. Twenty-three patients with advanced RCC have been treated with rIL-2 18 MIU/m²/day for 120 hours, followed by α-IFN 9 MU thrice weekly for 3 weeks. Seventeen patients completed at least one treatment cycle and were evaluated for response. We observed 6 major responses (1 CR and 5 PRs, 35%; 95% CI 17-59), and 5 SDs. Sites of response include lung, nodes and bone. Duration of responses is 12+ months for CR; 17, 16, 12+, 9 and 9 months for PRs. Median survival is 16 months. Toxicity related to rIL-2 was substantial, forcing to interrupt treatment in 11/23 patients. Most of these interruptions were due to cardiovascular toxicity, occurring even after reduction of rIL-2 dose to 9 MIU/m²/day in the last 11 patients. At this dose level, however, there was a significant reduction in fever, hypotension, oliguria, raise of s-creatinine, and PT elongation. The concurrent presence of eosinophilia, maintenance of high CD25+ cell count, and anti-thyroid antibodies seemed to be related to a better response. This regimen has been shown to be effective, but cardiovascular toxicity of rIL-2 remains a major problem.

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A SINGLE-CENTRE EXPERIENCE WITH CONTINUOUS INTRAVENOUS INFUSION OF RECOMBINANT INTERLEUKIN-2 ± LAK CELLS IN METASTATIC RENAL CELL CANCER

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Seventeen patients (pts) with metastatic renal cell cancer (RCC) were treated with recombinant interleukin-2 (rIL-2) by continuous i.v. infusion (CIVI) ± LAK cells following West's schedule (rIL2 18 MIU/m²/day d 1-5 and 12-16; leukapheresis on days 8-11 and LAK cell reinfusion on day 12, 13 and 15). Six of them did not receive LAK cells. Fifteen pts were evaluated for response: 1 CR and 2 PR were seen (20%, 95% CI 7-45). Eight further pts achieved transient stabilisation of disease. Responses were observed at any organ site except for bone. Duration of response was 11 and 7 mo (PR), 18 mo (CR). Cardiac toxicity caused exclusion from the study in 4 cases (with 1 toxic death). Subsequently, 9 pts were treated following a different induction schedule with the aim of reducing toxicity through tachyphylaxis. LAK cells were omitted and rIL-2 was given at 18 MIU/m²/day by CIVI d 1-5 and 8-12. Accrual was anticipately closed because of the excessive toxicity (5/9 toxic drop-outs) and the lack of evident antitumor activity (no objective response) . Again, cardiac toxic side effects were frequent and severe. Median follow-up for all pts is 42 mo. Median survival was 11.7 mo for the first group of pts and 7.8 mo for the second group (p= 0.06). Pts achieving at least SD at the end of maintenance (n=8) showed an impressive survival advantage (39 vs 8.5 mo; p= 0.0003). Tumor extent was inversely correlated with survival (p=0.01). Continuous infusion rIL-2 was confirmed to be moderately active in metastatic RCC, but is associated to severe cardiovascular toxicity.

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SINGLE-DOSE ANTIBIOTIC PROPHYLAXIS WITH TEICOPLANIN IN CANCER PATIENTS RECEIVING CONTINUOUS INFUSION INTERLEUKIN-2 THROUGH CENTRAL VENOUS CATHETER

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In our previous series of 22 patients (pts) treated with 105 courses of continuous infusion (CI) recombinant interleukin-2 (rIL-2) administered through central venous catheter (CVC) without antibiotic prophylaxis, we observed 7 major infections with 2 endocarditis by Staph. aureus (SA), causing definitive interruption of rIL-2 therapy. Thus, we treated 24 pts with advanced cancer receiving CI rIL-2 with single-dose antibiotic prophylaxis before the insertion of CVC. Teicoplanin was elected because of its high level of activity against Staphs. (even if methicillin-resistant) and was given at a dose of 400 mg as a slow i.v. infusion 1 hour before inserting CVC. Sixty CVCs were inserted; median permanence was 6 days (range 1-22). We observed 3 major infections (1 SA sepsis, 1 SA infection of insertion site, 1 pneumonia), with isolation of SA from CVC tip cultures in all cases. Tip cultures were positive in 39/60 cases (65%), 32/39 (82%) for Staph. epidermidis, 6/39 (15%) for SA, 1/39 (3%) for E.coli. Similar results were obtained from cultures of extravascular segments of CVC and skin cultures of insertion site during rIL-2 in usion and after removal of CVC. Although the number of infections and positive cultures was not significantly different from what previously observed without antibiotic prophylaxis, the absence of endocarditis and the decrease in SA colonization of CVC tips (6/39 vs 14/55) are relevant to support the use of antibiotic prophylaxis in cancer pts treated with CI rIL-2 through a CVC. Positive skin culture for SA during rIL-2 infusion seemed to have predictive value for subsequent infection.