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TREATMENT OF T CELL LYMPHOMA WITH MONOCLONAL ANTI-IDIOTYPE ANTIBODY. D.G. Maloney, H.T. Maecker, S. Takahashi, D. Czerwinski and R. Levy. Stanford Medical Center, Stanford CA 94305.

Epitopes formed by the combination of the alpha and beta chains of the T cell antigen receptor provide a clonotypic marker for monoclonal tumors of T cell origin. We report here the production and therapeutic use of a monoclonal anti-idiotype antibody against the T cell receptor of a patient with cutaneous T cell lymphoma. Balb/c mice were immunized with tumor cells and hybridomas screened for the ability to co-modulate CD3 then further selected for tumor specificity by cell staining and immunoprecipitation. HL1 precipitated the alpha and beta chains of the T cell receptor but not the CD3 complex from tumor cells. It bound to patient tumor cells, but not to other cloned T cell lines and less that 4 percent of cells in tonsil or blood. In vitro, HL1 had no effect on the incorporation of 3H-thymidine. Rapidly increasing skin lesions occurred following discontinuation of chemotherapy prior to antibody treatments. The patient was treated with antibody given IV three times each week for two, three week courses. The dose was escalated to 300 mg to obtain circulating antibody. Blood and skin tumor cells were rapidly coated with antibody. Serum samples were monitored for antibody level and circulating tumor cells analyzed by FACS. Skin biopsies documented a reduction in tumor burden. HL1 positive cells remained in the blood despite being coated with antibody. The patient had initial worsening then clearing of his skin lesions over the following four months. We conclude, that like anti-idiotype therapy of B cell malignancies, anti-idiotypic T cell antibodies hold promise as anti-tumor immunotherapeutic agents.

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ANTI-TRANSFERRIN RECEPTOR IMMUNOTOXIN (IT) THERAPY: PHASE-I INTRAPERITONEAL (*i.p.*) TRIAL. M.A. Bookman, S. Godfrey, K. Padavic, T. Griffin, J.P. Corda, T. Hamilton, R.F. Ozols, E.S. Groves. Fox Chase Cancer Center (FCCC), Philaladelphia, PA 19111; U. Mass. Medical School, Worcester, MA 01605; and Cetus Corp., Emeryville, CA 94608.

The transferrin receptor (TfR) is uniformly expressed on malignant, as well as normal cells, is efficiently internalized, and is a suitable target for IT delivery. The murine anti-TfR monoclonal antibody 454A12 was linked via a reducible disulfide bond to recombinant ricin A-chain (rRA, Cetus) to create 454A12-rRA. Efficacy was demonstrated in preclinical studies using a xenogeneic nude mouse model with human ovarian cancer (FitzGerald, *et al.* Cancer Res 47:1407,1987) and a syngeneic murine model with different anti-TfR ITs (Bjorn and Groetsema, Cancer Res 47:6639, 1987). A clinical trial was initiated for patients (pts) with ovarian, mesothelial, renal, and gastrointestinal cancer involving the peritoneal cavity:

Target Doses:	20 μg test dose day 1; then 5, 10, 25, 50, 100 μg/kg daily x 5 days *i.p.* in 2000 ml dialysate (1.5% dextrose)
Accrual (11/89):	10 pts treated at FCCC and U. Mass. Medical School
Maximum Dose:	20 μg test dose followed by 25 μg/kg x 5 doses
Toxicity:	IT-related: Hypoalbuminemia Gr1 (all pts) and malaise. Not clearly IT-related: Peritonitis (1 pt, 1 dose) and partial bowel obstruction (1 pt, 1 dose). No myelosuppression, mucositis, skin rash, or neurologic toxicity.
IT Levels:	Intact IT measured by sandwich ELISA (3 pts @ 5 μg/kg). *i.p.* levels sustained in 3 pts between 20 and 150 ng/ml x 5 days. Serum levels detectable in 1 pt between 3 and 10 ng/ml.
Response:	0 CR, 0 PR, 1 decreased ascites, 5 progressive disease.

Untreated ascites tumors were evaluated for TfR by immunohistochemical staining and immunofluorescent staining with flow cytometry. IT-mediated protein synthesis inhibition (IC_{50}) was measured by [^{3}H]-leucine incorporation @24 hrs. All tumors examined were TfR(+) and had IC_{50} values between 10 and 100 ng/ml. Data regarding formation of neutralizing antibodies are pending. We conclude that anti-TfR IT can be administered *i.p.* with acceptable toxicity to pts with cancer at doses which achieve detectable serum levels and with *i.p.* levels that exceed the *in vitro* IC_{50}. Dose escalation continues on this study to determine the spectrum of dose-limiting toxicity and obtain additional biological data.

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A PHASE II STUDY OF DACARBAZINE (DTIC), CISPLATIN (DDP), AND OUTPATIENT INTERLEUKIN-2 (IL-2) (RIDD-2) IN METASTATIC MALIGNANT MELANOMA (M.M.M.). L. Flaherty, W. Robinson, B. Redman, R. Gonzales, S. Martino, M. Kraut, M. Valdivieso, and A. Rudolph. Wayne State Univ., Detroit, MI., 48201, Univ. of Colorado, Denver, CO., 80220, and Cetus Corp., Emeryville, CA., 94608.

The tolerability of DTIC and outpatient IL-2 along with a median survival of 8.5 mos., and responses in visceral organs (ASCO, 7:254, 1988) in MMM, prompted the present ongoing phase II study of DTIC, DDP, and IL-2. DTIC (750 mg/M^2) IV over 30 min. and DDP (100 mg/M^2) IV over 30 min. are administered on Day 1. IL-2 24.0 x 10^6 IU/M^2 IV bolus is administered d12-16, d19-23 of each 28 day cycle. 25 patients (pts.) have been registered to date and 91 cycles of therapy have been evaluated for toxicity. Patient characteristics include median age-52 y.o. (16-74), males 13, females 12, performance status 0-1 in 21 pts., 2 in 4 pts. No pt. had prior chemotherapy. 17 pts. had visceral involvement. Toxicity consisting primarily of fatigue, anorexia, arthralgias, vomiting, fever and chills, necessitated 13 IL-2 dose reductions. The mean dose of IL-2 administered has been 21.3 x 10^6 IU/M^2. Renal toxicity (creatinine clearance <60cc/min.) has occurred in 11/91 courses. 24 pts. are evaluable for response with 2 CR's and 7 PR's (38% RR). 2 pts. have been rendered disease-free with additional surgery. CR's have occurred in soft tissue and lymph nodes. PR's have occurred in soft tissue, lymph node, lung, liver, spleen, and adrenals. DTIC and DDP did not interfere with the repeated generation of NK and LAK activity. This program has been tolerable and more effective than our prior efforts combining DTIC and IL-2.

IL-2 was provided by Cetus Corp., Emeryville, CA.

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RECOMBINANT HUMAN INTERLEUKIN 2 (IL2) + IL2 ACTIVATED LYMPHOCYTES (LAK) + ALPHA-INTERFERON (α-IFN) IN METASTATIC RENAL CELL CARCINOMA.

G. Stoter[1], S.H. Goey[1], C.J.A. Punt[1,3], C.R. Franks[2], C. Lamers[1], R.L.H. Bolhuis[1]. 1) Rotterdam Cancer Institute, Rotterdam, The Netherlands 2) EuroCetus BV, Amsterdam, The Netherlands 3) University Hospital, Nijmegen, The Netherlands

Sixteen patients (pts) with measurable metastatic renal cell carcinoma have been treated with daily continuous intravenous (c.i.v.) infusion of IL2 18 MIU/m^2/day, d 1-5. Leukapheresis is performed at d 7-9. LAK is given following leukapheresis at d 12-14 with IL2 d 12-16. α-IFN 5 MU/m^2/day i.m. is given at d 12-15. This cycle is repeated at day 36. Patients with stable disease or response receive 4 maintenance cycles consisting of IL2 18 MIU/m^2/day c.i.v., d 1-4 and α-IFN 5 MU/m^2/day i.m. d 1-4. Cycles are repeated every 4 weeks. There were 11 males and 5 females with a median age of 52 (39-65) and a Karnofsky index of 100 (80-100). All patients had undergone nephrectomy of the primary tumor. Metastatic sites were lung, pleura, lymph nodes, liver, mesentery, and retroperitoneum. Among 12 evaluable pts, we observed 4 (33%) complete responses (CR), and 3 pts have stable disease while still on therapy. All responses occurred in lung and pleural metastases. One CR relapsed after 5 months. The remaining 3 CRs are lasting 4$^+$, 8$^+$ and 11$^+$ months. Side effects were similar to those expected from each treatment component alone. One patient developed a fatal myocardial infarction between cycle 1 and 2 with a ventricular septum defect. These preliminary results show a high CR rate as compared to our previous experience with IL2 alone and IL2 + LAK.

N.B.: 1 Cetus Unit = 6 International Units (IU)