Cancer Investigation

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Table 1

Level	Taxol dose, mg/m^2	No. of pts/cycle	Gr. 4 neutropenia/cycle	Gr. 4 thrombocytopenia/ cycle	Other side effects (grade)
I	120	3/14	1/14	0	1 pneumonia (2)
II	135	3/17	7/17	4/17	1 C. diff. (2); 1 leucopenic fever
III	150	3/15	5/15	2/15	1 leucopenic fever
IV	175	6/18	5/18	1/18	1 N/V (4)

from analysis due to lack of information. A total of 64 cycles have been given to the patients. The dose-limiting toxicity was defined as grade 3 or worse nonhematologic toxicity or neutropenic sepsis, or grade 4 neutropenia greater than 5 days. If any patient developed a dose-limiting toxicity, subsequent patients were entered to the same level of Taxol. The side effect profiles of the 15 patients are shown in the table.

Alopecia was universal. Nausea/vomiting was usually mild or moderate except for 1 patient. Myelosuppression was accumulative. No toxic death was observed. There was 1 complete remission (CR), 5 partial remission (PR) in 6 breast cancer patients; 3 CR and 1 PR in 4 sarcoma patients; PR in 1 patient with adenoidcystic carcinoma; the other 4 patients did not respond. In summary, ICE–T is a very active and well-tolerated regimen. The study is continuing.

BIBLIOGRAPHY

Fields KK, Elfenbein GJ, Saleh RA, et al: Ifosfamide, carboplatin, and etoposide for induction and high-dose chemotherapy: Focus on breast cancer and lymphoma. Hematol Oncol 10:61–74, 1992.

Hsieh R-K, Chang AY-C, Boros L, Asbury R: Phase II study of ifosfamide, carboplatin, and etoposide in patients with advanced non-small cell lung cancer. Am J Clin Oncol 17:509–513, 1994.

Loehrer PJ, Lauer R, Roth BJ: Salvage therapy in recurrent germ cell cancer: ifosfamide and cisplatin plus either vinblastine or etoposide. Ann Intern Med 87:540–547, 1988.

Rowinsky EK, Cazenave LA, Donehower RC: Taxol: a novel investigational antimicrotubule agent. J Natl Cancer Inst 82:1247–1259, 1990.

Smith IE, Perren TJ, Ashley SA, et al: Carboplatin, etoposide, and ifosfamide as intensive chemotherapy for small-cell lung cancer. J Clin Oncol 8:899–905, 1990.

Van Zandwijk N, ten Bokkel Huinink WW, Wanders J, et al: Dose finding studies with carboplatin, ifosfamide, etoposide and mesna in non-small cell lung cancer. Semin Oncol 17(suppl 2):16–19, 1990.

53. CHEMOIMMUNOTHERAPY OF LOW-GRADE LYMPHOMA WITH THE ANTI-CD20 ANTIBODY IDEC–C2B8 IN COMBINATION WITH CHOP CHEMOTHERAPY

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The incidence of non-Hodgkin's lymphoma (NHL) is increasing in the United States. More than 50,000 new cases of NHL are projected to occur in the U.S. for 1995, with approximately 42% of these cases being of a low-grade or follicular histology (International Working Formulation A, B, C, or D). Although low-grade lymphomas are responsive to standard chemotherapy, the majority of patients are not cured by this approach. In fact, the best results from high-dose systemic chemotherapy with total-body irradiation in the setting of purged autologous bone marrow transplantation (ABMT) produce recurrence-free survival in only 40–75% of patients (Gribben et al; Johnson et al) with a median follow-up of approximately 4 years. Molecular research has identified the bcl-2 protooncogene as being associated with the t(14;18) chromosomal translocation of follicular, low-grade lymphomas. This t(14;18) leads to movement of the bcl-2 gene from 18q21 to 14q32 (immunoglobulin heavy chain locus) and results in increased transcription and accumulation of high levels of bcl-2 protein. Recent research has demonstrated that bcl-2 overexpression may lead to multidrug resistance, independent of the P170 glycoprotein, by causing

resistance to apoptosis by a variety of chemotherapeutic agents including certain alkylating agents, doxorubicin, glucocorticoids, and vincristine (Hsu et al). For patients with low-grade lymphoma, bcl-2 status posttherapy may not only have prognostic value, but may also serve as a marker to monitor minimal residual disease. Extensive research by Gribben et al has demonstrated that no patient cleared bcl-2 positivity in marrow following induction or salvage chemotherapy (including 6 cycles of standard-dose CHOP), and that residual bcl-2 positive cells in reinfused purged autologous bone marrow appear to be associated with a 7.5-fold risk of relapse in patients undergoing ABMT for low-grade lymphoma. Unfortunately a large number of patients with low-grade lymphoma are elderly or have bone marrow which is unable to be purged to polymerase chain reaction (PCR) negativity and would therefore not be optimal candidates for ABMT. Because of this, new therapeutic strategies with improved antitumor activity and acceptable toxicity need to be developed with the goal being achievement of a molecular complete remission with no detectable bcl-2 rearrangement in marrow or blood by sensitive PCR methods. Preliminary data from a novel chemoimmnotherapeutic approach of treating low-grade lymphoma with standard-dose CHOP and IDEC–C2B8 (a chimeric anti-CD20 antibody) is being presented at this time. IDEC–C2B8 has previously been shown to have antitumor activity with mild to moderate toxicity as a single agent in patients with relapsed low-grade and follicular lymphoma. In a recent IDEC–C2B8 multidose (375mg/ m^2 q week × 4) phase II trial, a 50% response rate (17 of 34 relapsed patients) lasting 4.4 to greater than 15.5 months was achieved (Maloney et al.). Mechanisms of action of IDEC-C2B8 include complement-mediated cytotoxicity, antibody-dependent cellular cytotoxicity, induction of apoptosis (in vitro data), and synergistic antitumor activity with certain chemotherapeutic agents (including doxorubicin). The rationale for combination of IDEC–C2B8 with CHOP includes: non-cross-resistant mechanisms of action, individual efficacy, nonoverlapping toxicities, and known synergy with doxorubicin. In the current trial, IDEC–C2B8 is given at a dose of 375 mg/m^2 on weeks 1 (2 infusions), 7, 13, 20, and 21 for a total of 6 doses. CHOP chemotherapy (cyclophosphamide 750 mg/m^2 i.v. × 1, doxorubicin 50 mg/m^2 i.v. × 1, vincristine 1.4 mg/m^2 i.v. × 1 (up to maximum of 2 mg), prednisone 100 mg/m^2/day p.o. for 5 days) is given on weeks 2, 5, 8, 11, 14, and 17 for a total of 6 cycles. Currently 27 patients have entered on this study and data are available for 14 patients, 11 of whom have completed all scheduled therapy. Of the 3 remaining patients, one was registered but never treated secondary to rapid onset of CNS disease, the second refused further therapy following 5 cycles of CHOP and 4 doses of IDEC–C2B8 due to steroid-induced severe depression (achieved a partial remission—PR), and the third was taken off study after 2 cycles of CHOP and 2 doses of IDEC–C2B8 following surgery for cervical osteomyelitis (achieved a PR). Characteristics of these 14 patients include: 6 males/8 females, 80% stage III/IV at diagnosis, median age 59 (range of 35–75), 12 previously untreated, IWF A = 4, IWF B = 4, IWF C = 5, other low-grade = 1. Adverse events included nausea, neutropenia, pain, fatigue, vomiting, fever, alopecia, constipation, and peripheral neuropathy. Sixty-one events were attributed to CHOP (80% grade 3 and 20% grade 2) and 18 to IDEC–C2B8 (25% grade 2 and 75% grade 1). The latter consisted primarily of flulike symptoms, usually associated with the first of six infusions. No human anti-mouse or anti-chimeric antibody responses (HAMA/ HACA) nor unexpected toxicities have been observed for the combination of CHOP and antibody. Overall response rate for the 11 patients completing all scheduled therapy is 100% (8 complete remission—CR and 3 PR). These responses are ongoing with a median observation time of 9 months. Four patients found to be positive for bcl-2 by PCR prior to therapy (3 in peripheral blood and bone marrow, 1 in peripheral blood alone) converted to bcl-2 negativity by completion of therapy. The three patients achieving PCR negativity in marrow have undergone unpurged autologous bone marrow harvesting at time of count recovery with the pooled bone marrow specimens confirming bcl-2 negativity. Current efficacy and toxicity data appear encouraging and the finding of molecular remissions by PCR suggests that the antitumor activity of CHOP and IDEC–C2B8 is superior to CHOP therapy alone. This study is onging and accrual of 30 evaluable patients is planned.

BIBLIOGRAPHY

Czuczman M, Grillo-Lopez AJ, Saleh M, et al: Phase II clinical trial of IDEC–C2B8/CHOP combination therapy in low-grade lymphoma: preliminary results, Proc ASCO 14:401 (#1261), 1995.

Demidem A, Hanna N, Hariharan H, et al: Chimeric anti-CD20 antibody (IDEC–C2B8) is apoptotic and sensitizes drug resistant human B-cell lymphomas and AIDS related lymphomas to the cytotoxic effect of CDDP, VP-16, and toxins. FASEB 9: A206, 1995.

Gribben JG, Freedman AS, Neuberg D, et al: Immunologic purging of marrow assessed by pcr before autologous bone marrow transplantation for B-cell lymphoma. N Engl J Med 325:1525–1533, 1991.

Gribben JG, Freedman AS, Woo SD, et al: All advanced stage non-Hodgkin's lymphomas with a polymerase chain reaction amplifiable breakpoint of bcl-2 have residual cells containing the bcl-2 rearrangement at evaluation and after treatment. Blood 12:3275–3280, 1991.

Gribben JG, Neuberg D, Freedman AS, et al: Detection by polymerase

chain reaction of residual cells with the bcl-2 translocation is associated with increased risk of relapse after autologous bone marrow transplantation for B-cell lymphoma. Blood 81: 3449–3457, 1993.
Hsu B, Marin M, Brisbay S, et al: Expression of bcl-2 gene confers multidrug resistance to chemotherapy-induced cell death. Cancer Bull 46:125–129, 1994.
Johnson PWM, Price CGA, Smith T, et al: Detection of cells bearing the t(14;18) translocation following myeloablative treatment and autologous bone marrow transplantation for follicular lymphoma. J Clin Oncol 12:798–805, 1994.
Maloney DG, Bodkin D, Grillo-Lopez AJ, et al: IDEC–C2B8: final report on a phase II trial in relapsed non-Hodgkin's lymphoma. Blood 84:169a (#661), 1994.
Maloney DG, Liles TM, Gzerwinski DK, et al: Phase I clinical trial using escalating single-dose infusion of chimeric anti-CD20 monoclonal antibody (IDEC–C2B8) in patients with recurrent B-cell lymphoma. Blood 84:2457–2466, 1994.

54. USE OF RADIOIMMUNODETECTION WITH CEA-SCAN™ IN THE PREOPERATIVE EVALUATION OF PATIENTS WITH COLORECTAL AND BREAST CANCER

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The ability of CEA-Scan™ to detect CEA-expressing tumors such as colorectal, breast, and lung cancer has been investigated in clinical trials over the past few years. The results of two multicenter trials (2) are discussed in this paper, one which evaluates the role of CEA-Scan in planning for resection of recurrent colorectal cancer (CRC); and the other, the safety and efficacy of CEA-Scan in the preoperative evaluation of breast and axillary nodes in breast cancer (BC). CEA-Scan was provided as an instant, ready-to-label kit. Patients with colorectal cancer and primary operable breast cancer were injected with 1 mg ^{99m}Tc-labeled Fab′ fragment of the murine anti-CEA IMMU-4 monoclonal antibody (CEA-Scan, Immunomedics, Inc., Morris Plains, NJ) labeled with 20–30 mCi ^{99m}Tc. Planar imaging was performed at 4–8 and 18–24 h postinjection. SPECT was performed at 4–8 h postinjection. Serum for HAMA analysis was obtained at baseline, 4–6 weeks, and 3–4 months postinjection.

Colorectal cancer: Curative resection of recurrent or metastatic CRC results in a 5-year survival rate of 25–30% (4). While radioimmunodetection (RAID) has been reported to accurately image CRC, its role in the preoperative patient evaluation for resection has not been established. A 20-center prospective clinical trial was undertaken in patients with CRC to determine the imaging efficacy, clinical utility, and safety of RAID using CEA-Scan. Ten adverse events were reported, only one of which was potentially serious (seizure in a patient with a long-standing history of hypertension, 1 day post-antibody infusion). The other adverse events—chills, eosinophilia, bursitis, nausea, low-grade fever, headache, rash, subdermal roughness, and "upset" stomach—were transient, mild, and judged remotely or not related to the antibody infusion by the investigator.

The ability to predict tumor resectability was studied in 208 of 210 patients with known or suspected CRC, who had the results of CT or CEA-Scan imaging correlated with surgery. Curative resectability (R) was based on the presence of ≤4 liver lesions and <2 regions of involvement. Nonresectability (NR) was based on >4 liver lesions or ≥2 regions of involvement (1–4). No evidence of disease (NED) was based on the absence of disease by either CT, CEA-Scan, or surgery. In 208 assessable patients, overall accuracy for predicting R, NR, or NED was higher for CEA-Scan, 124/208 (60%), than CT scan, 97/208 (47%), $p = 0.0014$, McNemar's test. In 50 patients in whom CT and CEA-Scan were concordant for R, the prediction of R was accurate in 31 patients (61%); and in 16 patients in whom both tests were concordant for NR, 15 patients (94%) were confirmed NR at surgery, thus obviating the need for additional diagnostic modalities. In 71 patients in whom the two tests were discordant, CEA-Scan was correct more often than CT; CEA-Scan: 49/71 (69%) versus CT: 22/71 (22%). Since the liver is a common site for metastases in CRC, the subgroup of patients who might benefit from detection of resectable liver lesions was also examined. CEA-Scan was more accurate in predicting R, NR, NED overall than CT, 47/100 (47%) versus 33/100 (33%), $p = 0.016$, McNemar's test.

In conclusion, (*a*) CEA-Scan more accurately predicted resectability, nonresectability, and disease-free status than CT in patients with known or occult colorectal cancer. (*b*) Using CEA-Scan in conjunction with CT results in statistically significant superior predictions of surgical outcome compared to CT alone. (*c*) Based on this analysis, certain decision rules for the management of patients with potentially resectable colorectal cancer can be proposed: When both CT and CEA-Scan are positive for a lesion or are confirmatory in establishing nonresectability, the managing physician can proceed with confidence in assuming