Modulation of Clinical Drug Resistance in a B Cell Lymphoma Patient by the Protein Kinase Inhibitor 7-Hydroxystaurosporine: Presentation of a Novel Therapeutic Paradigm

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ABSTRACT

Emerging evidence suggests that apoptosis is an important mechanism of tumor cell death from antineoplastic therapy. 7-hydroxystaurosporine (UCN-01) is a novel protein kinase inhibitor that increases chemotherapy-induced apoptosis in vitro and is in early phases of clinical development. In this report, we present a 68-year-old patient with chemotherapy-resistant lymphoma treated with UCN-01 and chemotherapy. He had a stage IV plasmacytoid lymphoma that failed to enter remission with high-dose EPOCH II (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin) chemotherapy. Due to disease progression and transformation to large cell lymphoma in the liver and bone marrow, he received UCN-01. Four weeks later, he received “standard-dose” EPOCH because of progression, developed severe neutropenia for 9 days, and expired from “standard-dose” EPOCH because of progression, developed severe neutropenia for 9 days, and expired from...
phoma. Since diagnosis, he had been observed with waxing and waning adenopathy but without systemic symptoms or organ compromise. Evaluation at the National Cancer Institute revealed new onset hypercalcemia, night sweats, weight loss, and fatigue. Staging showed lymphoma in the bone marrow and whole body computerized tomography (CT) showed multiple small pulmonary nodules, retroperitoneal adenopathy, a splenic nodule, and moderate hepatosplenomegaly. Other laboratory tests, including parathyroid hormone were normal. Treatment was begun on an experimental protocol of high-dose EPOCH II chemotherapy (mg/m²/continuous intravenous infusion for 96 h), 60 doxorubicin, 300 etoposide, 1.6 vincristine, and 60 mg/m²/day prednisone p.o. for 4 days, alternating with 2000 mg/m² cyclophosphamide every 12 h for 2 doses, each given every 3 weeks with G-CSF (5 mg/m² cyclophosphamide every 12 h for 2 doses, each given normal neutrophil count (5,350 cells/l), and blood chemistries globin, 5.5) and thrombocytopenia (37,000 platelets/l) were normal. Treatment was discontinued after four of six planned cycles due to thrombocytopenia (<50,000 platelets/µl), profound fatigue, and diminishing performance status. Restaging evaluation after cycle 4 showed resolution of the adenopathy and pulmonary and splenic nodules but persistent splenomegaly and positive bone marrow biopsies. The patient was scored as a partial response and was observed. The thrombocytopenia resolved within 6 weeks of discontinuation of treatment, and the patient gradually regained activity over the next 3 months.

Approximately 10 months later, the patient developed progressive neutropenia (absolute neutrophil count <500 cells/µl) and thrombocytopenia with an elevated LDH. CT scans showed progressive splenomegaly and adenopathy, and bone marrow biopsies showed lymphoma with moderate hyperplasia and increased megakaryocytes. He underwent a therapeutic splenectomy and recovered his neutrophil (>1,000 cells/µl) and platelet (>150,000/µl) counts over the next 4 days, and the LDH returned to normal. On pathological review, the spleen showed histological transformation to a large B cell lymphoma. Over the next 2 months, the patient developed elevated hepatic enzymes (up to five times the normal amount), and a liver biopsy showed large B cell lymphoma.

Therapeutic options were discussed and the patient elected to receive UCN-01 (53 mg/m²/day for 72 h) on a phase I protocol. He acutely tolerated the first cycle of UCN-01 but was admitted to the hospital 4 weeks later with profound fatigue and dehydration. Hematological evaluation showed anemia (hemoglobin, 5.5) and thrombocytopenia (37,000 platelets/µl) with a normal neutrophil count (5,350 cells/µl), and blood chemistry showed an increase in alkaline phosphatase (252 units/L), bilirubin (1.8 mg/dl), and LDH (638 units/L; normal, <225 units/L). CT showed progressive hepaticomegaly and diffuse adenopathy, and a bone marrow biopsy showed diffuse replacement with large B cell lymphoma. Due to rapidly worsening disease, the patient received modified doses of “standard” EPOCH chemotherapy: because of the recent UCN-01 and liver abnormalities, cyclophosphamide was omitted and vincristine was administered at 75% dose (16). A total dose (mg/m²) of 40 doxorubicin, 200 etoposide, and 1.2 vincristine was administered as continuous infusions over 96 h, and 60 prednisone was administered p.o. for 5 days. G-CSF (5 µg/kg, s.c. twice per day) was begun 24 h after chemotherapy. Laboratory studies on treatment day 1 were LDH, 1,358 units/L; total bilirubin, 9.7 mg/dl (direct, 6.8); and absolute neutrophil count, 5,520 cells/µl. On day 3, the LDH increased to 5,851 units/L, and the total bilirubin had decreased to 2.8 mg/dl. By day 7, the LDH had normalized, but the patient became neutropenic and was transferred to the intensive care unit with fever and hypotension. Evaluation revealed a tender abdomen and CT showed a diffusely thickened bowel consistent with neutropenic enterocolitis. Blood cultures showed Candida krusei, and the patient remained unstable despite broad spectrum antibiotics, blood pressure support, and intubation. Although the neutrophils recovered by day 16, the patient expired on day 23 from uncontrolled C. sepsis. An autopsy was obtained.

MATERIALS AND METHODS

Immunohistochemistry. Immunohistochemical studies were performed on paraffin-embedded tissue sections with a panel of monoclonal antibodies that included the B cell marker CD20 (L26) and T cell marker CD3 (polyclonal; Dako Corp., Carpinteria, CA). In brief, after deparaffinization, the slides were placed in a microwavable pressure cooker containing 1500 ml of 10 mM citrate buffer at pH 6.0 containing 0.1% Tween 20 and microwaved (model R4A80; Sharp Electronics, Mahwah, NJ) for 40 min at 700 W. Immunohistochemistry was then performed on an automated immunostainer (Ventana Medical Systems, Inc., Tucson, AZ) using the manufacturer’s paraffin slide protocol.

Molecular Analysis. Formalin-fixed paraffin-embedded tissue samples were sectioned, digested in a buffer (50 mM Tris (pH 8.0), 150 mM NaCl, 5 mM EDTA, 1% SDS) containing proteinase K (Life Technologies, Inc., Rockville, MD) and RNase A (Sigma, St. Louis, MO), and incubated at 55°C for 48–72 h. When digestion was complete, DNA was purified by phenol/chloroform extraction and precipitated with ammonium acetate (5.0 µl) and 100% ethanol (17). The pellets were dried and then dissolved in double-distilled water, and the DNA was quantitated by absorbance at 260 nm.

To determine clonality of the IgH gene, PCR assays were performed on each sample using the VH framework 3 and JH consensus primers as reported by Segal et al. (18). PCR was performed using 1 µg of DNA template in 1× PCR buffer (10 mM Tris-HCl, 50 mM KCl, 2.5 mM MgCl₂, 200 µM deoxynucleotide triphosphates (each), and 0.5 µM primers (each)). The reaction was initiated with 0.5 U of Taq polymerase (Perkin-Elmer-Cetus, Norwalk, CT) treated with TaqStart antibody (Clontech Laboratories, Palo Alto, CA), and PCR was continued for 35 cycles (94°C, 1 min; 56°C, 1 min; and 74°C, 1 min) with a final extension of 7 min at 74°C (19). Subsequent to amplification, the products were separated by 16% nondenaturing PAGE (Bio-Rad, Richmond, CA) and visualized by UV light after ethidium bromide treatment. Control PCR to glyceraldehyde phosphate dehydrogenase was also performed to assess the integrity of extracted DNA for amplification.

Pharmacokinetics. Blood samples were obtained for UCN-01 analysis at 0, 4, 12, 24, 48, and 72 h from the start of the UCN-01 infusion and at 2, 12, and 24 h and 21 days from the end of the infusion. Samples were also obtained at 34, 36, 38, 46, and 48 days from the start of the UCN-01 infusion, which corresponded to 0, 48, and 96 h and 12 and 14 days from the start of the EPOCH infusion. Saliva samples for UCN-01 de-
termination were obtained at 24 and 48 h from the start of the UCN-01 infusion and on days 24, 31, and 33 from the end of the UCN-01 infusion. The latter two saliva samples corresponded to 0 and 48 h from the start of the EPOCH infusion. Pharmacokinetic parameters for UCN-01 were obtained by fitting a two-compartment open linear model to the data. These calculations were made with the use of ADAPT II using a weighted least squares estimator. These parameters were calculated using data collected before the initiation of EPOCH chemotherapy. The changes in pharmacokinetic parameters were estimated allowing an instantaneous change in clearance and volume of distribution during the EPOCH infusion.

UCN-01 concentrations were determined by reverse-phase HPLC using the Hewlett Packard 1090 series II liquid chromatograph equipped with a photodiode-array detector and an HP 1046A programmable fluorescence detector (Hewlett-Packard, Palo Alto, CA). Calibration curves of 4–200 ng/ml and 200–20,000 ng/ml were prepared for the determination of UCN-01 from saliva and plasma, respectively. A sample of 250 μl of either plasma or saliva was prepared by protein precipitation with 1.0 ml of acetonitrile. Umbelliferone was added as the internal standard. Separation was performed using a Waters (Milford, MA) Nova-Pak Phenyl 3.9 × 150 mm column. The mobile phase of acetonitrile and 0.05 m ammonium acetate (pH 4.15) was pumped at a flow rate of 1.0 ml/min using a gradient profile. The total run time was 20 min per sample. UCN-01 was quantitated using fluorescence detection for saliva samples. The excitation and emission wavelengths monitored were 290 nm and 400 nm, respectively. UCN-01 was quantitated using UV absorption for plasma samples. UCN-01 was detected at 295 nm, and umbelliferone was detected at 323 nm.

Doxorubicin (Sigma) concentration was measured by an isocratic reverse-phase HPLC method with fluorescence detection. Daunorubicin was added as an internal standard. Plasma samples were prepared by solid phase extraction and eluted with 9:1 methanol:formic acid. CSF samples were extracted with 5% perchloric acid. The mobile phase consisted of 79:21 0.4 m ammonium formate:acetonitrile at pH 4.0 and a flow rate of 2 ml/min. An excitation wavelength of 480 nm and emission wavelength of 595 nm were used for fluorescence detection. A µBondapak Phenyl column (Waters Corp.) with a PS-GU Phenyl 5-µ guard column (Thomson Instrument Company, Springfield, VA) was used. Analysis was done using Millenium software (Waters Corp.). The limit of detection was 5 nm, limit of quantitation was 10 nm, and coefficient of variation was ≤10%. Etoposide was quantitated using a previously published reverse-phase HPLC method (20). A C18 column was used for separation and UV detection at 254 nm. The standard curves ranged between 500 ng/ml and 30,000 ng/ml with coefficients of variation <20%.

RESULTS

Light Microscopy. The diagnosis of a low-grade lymphoma with plasmacytoid features was initially made from a cervical lymph node. A bone marrow biopsy and aspiration was obtained six years later, immediately before high-dose EPOCH II chemotherapy, showed multiple aggregates of small lymphocytes with a B cell λ phenotype. Repeat bone marrow biopsies obtained 1 and 6 months after EPOCH II showed a similar extent of involvement by a low-grade B cell lymphoma. Histological assessment of the spleen, liver, and bone marrow 1 year after EPOCH II showed diffuse involvement by small and large B cell lymphoma consistent with transformation to diffuse large B cell lymphoma. A bone marrow biopsy obtained immediately after UCN-01 also showed diffuse replacement by small and large B cell lymphoma.

At the time of autopsy, multiple tissues were examined by histology and immunohistochemistry. Sections of the liver showed perportal fibrosis, mild chronic inflammation, cholestasis with bile plugging, and microvesicular hepatocellular steatosis but no evidence of tumor. The bone marrow was markedly hypocellular with scattered small CD3 + T cells and no evidence of L26+ B cells or lymphoma. Interestingly, sections of lymph nodes showed near complete lymphocyte depletion with fibrosis, vascular dilation, and prominent hemosiderin deposition. Nearly all remaining viable lymphocytes stained with CD3 and no L26+ B cells were present. Sections from retroperitoneal lymph nodes showed large, amorphous, hyalinized areas. No other organs or tissues examined showed histological evidence of lymphoma.

Pharmacokinetics. The patient received a single cycle of UCN-01 at 53 mg/m²/day infused over 72 h on our phase I study. This dose exceeded the maximum tolerated dose, which was limited by hyperglycemia, nausea and vomiting, and hypoxia. Pharmacokinetic results from prior patients showed UCN-01 to be highly protein bound (>99%) and hence to have a prolonged half-life. The present patient achieved an end infusion UCN-01 concentration of 25,970 ng/ml (48 μmol/L) with a terminal phase rate constant of 0.0003 L/h and a terminal T1/2 > 1,000 h (>40 days; Fig. 1). Due to the long T1/2 of UCN-01, a reasonably high UCN-01 concentration of 17,449 ng/ml (36 μmol/L) was present on the first day of EPOCH administration, 34 days after beginning the UCN-01. Of potential significance, the terminal phase rate constant appeared to transiently increase to 0.0043 L/h after the start of EPOCH but returned to the preexistent rate based on serum samples obtained 8 days after completion of EPOCH.

Because UCN-01 is highly protein bound, we were interested in assessing the “free” drug concentration to obtain a measure of the biologically available UCN-01. The concentration of UCN-01 in saliva was used as a surrogate for free drug based on the absence of the principal serum-binding protein acid-1 α-glycoprotein in salivary secretions (6). The accuracy of saliva concentrations is currently being validated in other samples by comparison to a high-speed centrifugation technique for the measurement of free drug in serum. In the present patient, the saliva concentration was 99.5 ng/ml (206 nmol/L) at 48 h, 33.5 ng/ml (69 nmol/L) at 27 days, and 10.7 ng/ml (22 nmol/L) at 34 days after the start of the UCN-01 infusion (Fig. 2). On the second day of EPOCH administration (36 days after UCN-01 initiation), the saliva concentration of UCN-01 was 22 ng/ml (46 nmol/L), which is within the range (10–40 nmol/L) of UCN-01 observed to abrogate the G2 checkpoint and to be synergistic with chemotherapy in vitro (10–13).

The C50 of doxorubicin and etoposide were measured to determine whether anticipated plasma concentrations were achieved. However, we did not measure plasma concentrations...
of vincristine because the expected plasma concentrations would have been at the limit of detection (21). At the administered doxorubicin and etoposide doses of 10 and 50 mg/m²/day, respectively, the Cₚₛₛ were approximately 7 nmol/L and 5.19 μmol/L, respectively. For comparison, the mean doxorubicin and etoposide Cₚₛₛ from six other patients with normal hepatic function who had received the same drug dose-rates were (± SD) 9.1 ± 3.5 nmol/L (range, 6.7–16.8) and 2.8 μmol/L (range, 2.5–3.2), respectively (22). These results show that the Cₚₛₛ of doxorubicin and etoposide were not significantly altered by the presence of UCN-01 or decreased hepatic function (direct bilirubin, 6.8 mg/dl) and indicate that the patients’ clinical response and hematopoietic toxicity were not due to altered pharmacokinetics of the cytotoxic drugs.

Molecular Analysis.  IgH PCR assays were performed to assess the presence of minimal residual disease. Fig. 2 shows the presence of a strong monoclonal band of identical size in all premortem biopsies from the lymph node, spleen, and liver. At autopsy, faint monoclonal bands could still be generated from two of six lymph nodes but not from the liver; amplifiable DNA was not present in the bone marrow samples. To confirm the identity of the “monoclonal” bands from the positive tissues, they were sequenced and found to be identical (data not shown). The low-level expression and the absence of immunohistochemically detectable B cells (see below) suggest the presence of few if any viable tumor cells.

Effects on B and T Cells.  The striking effect of UCN-01 and EPOCH on the patients’ lymphoma suggested the combination might be quite toxic to normal lymphocytes as well. To help assess this, we performed immunohistochemistry using B cell (L26) and T cell (CD3) antibodies and immunoglobulin and T cell gene rearrangements by PCR on bone marrow, spleen, liver, and lymph nodes. At autopsy, the lymph nodes only showed scattered T cells and no B cells by immunohistochemistry. In addition, Fig. 2 shows that the initial lymph node biopsy and the spleen had a typical polyclonal immunoglobulin ladder background consistent with normal B cells, whereas the lymph nodes obtained at autopsy lacked the polyclonal ladder, indicating significant loss of normal B cells.

We also studied the effect of UCN-01 and EPOCH on the patient’s peripheral blood lymphocytes. Before beginning any therapy, the patient had a moderately reduced absolute lymphocyte count of 1,332 cells/μl; the phenotype of these included 345 CD4 [the majority of which (323) were CD45RO], 204 CD8, 339 NK cells, and 286 B cells. Although the patient began EPOCH II with low peripheral lymphocyte counts, he generally recovered to his baseline counts by the end of each cycle (Fig. 3A). Furthermore, there was no significant change in the peripheral lymphocyte count by day 28 after administration of UCN-01 (Fig. 3B). However, it is of interest that he had a dramatic reduction in peripheral lymphocytes from a baseline of 1,160 down to 50 cells/μl by day 7 after EPOCH. Unexpectedly,
he had no evidence of peripheral lymphocyte recovery by day 23 of EPOCH, despite a brisk recovery of the neutrophils to 10,000 cells/µl. These results suggest that UCN-01 significantly sensitized normal lymphocytes to relatively modest doses of chemotherapy and may have affected lymphocyte precursors as well.

**DISCUSSION**

A number of important new discoveries are challenging long-held concepts relating to tumor cell death and drug resistance. With the emerging indication that apoptosis is an important response of cells to antineoplastic agents, attention has turned to understanding its regulation (1–5). Although the biochemical mechanisms involved in apoptosis are still poorly understood, a number of proteins involved in regulation of the cell cycle such as p53 and bcl-2 have been shown to modulate the apoptotic response in vitro and have been associated with clinical drug resistance in lymphomas (5, 23–25). Protein kinases also function as important regulators of cell cycle checkpoints, and nonspecific antagonists such as staurosporine have been shown to induce apoptosis (14). We have been interested in the clinical development of UCN-01 because it is a potent protein kinase antagonist, particularly against the Ca^{2+}-dependent protein kinase C (IC_{50} = 30 nM; Refs. 26–28). Furthermore, UCN-01 has demonstrated significant in vitro inhibition of tumor cell growth and antitumor activity in human tumor xenografts and murine tumor models (9).

In this report, we describe for the first time the clinical effects of UCN-01 and chemotherapy in a patient. A striking result from this case was the achievement of a pathologically complete remission with UCN-01 and EPOCH chemotherapy in a patient with bulky and chemotherapy-resistant lymphoma. Of significance, the patient had previously failed to enter remission after high-dose chemotherapy, which included the same agents and schedules albeit at significantly higher doses (EPOCH II; 3-fold greater doxorubicin and etoposide, 2.7-fold greater vincristine over 2 cycles, and an additional 8000 mg/m² cyclophosphamide over 2 cycles). After standard-dose EPOCH, the patient developed prolonged neutropenia and enterocolitis, toxicities which may have been due to his underlying clinical condition and/or enhancement of EPOCH toxicity by UCN-01 (6).

A potentially significant observation was the effect of EPOCH on the pharmacokinetics of UCN-01. A seeming disadvantage of UCN-01 is the high protein binding and prolonged terminal half-life. As such, total plasma concentrations are a poor measure of free drug, and significant amounts of UCN-01 may be present for weeks after its administration. Fig. 1 shows the concentration of UCN-01 in plasma and saliva over time and demonstrates a transient increase in UCN-01 clearance after the start of EPOCH. The increased clearance of UCN-01 could be explained by competitive binding between one or more of the EPOCH drugs and UCN-01 for plasma protein binding sites; in support of this are in vitro studies showing competitive binding between etoposide and UCN-01 (our unpublished observations). Less likely, UCN-01 may have been released from dying tissues.
resulting in a temporary increase in free drug concentration. However, it is clear from pharmacokinetic data obtained from other patients that the increased clearance is not due to plasma concentrations reaching the UCN-01 binding $K_m$ (data not shown). These new data suggest that the pharmacokinetic profile of UCN-01 may be advantageous, allowing extended drug exposure and transient increases in free drug concentrations during chemotherapy administration.

We believe these clinical results indicate that UCN-01 modulated the sensitivity of the patient’s tumor cells to the effects of EPOCH chemotherapy. Indeed, we know of no precedent for any chemotherapy to produce a complete remission in a patient with disease resistant to the same drugs and schedule. Furthermore, although the patient had undergone a histological transformation that arguably might have a different sensitivity pattern (though usually more resistant), both the large and original small cell components of his disease were pathologically eliminated. A potential explanation for this response (which we considered) was a pharmacokinetic interaction between UCN-01 and EPOCH leading to a markedly increased concentration of EPOCH drugs. To assess this possibility, we measured the $C_{ss}$ of doxorubicin and etoposide and found them to be within the range of control patients who had received standard dose EPOCH in an earlier study (22).

To fully characterize the patient’s pathological response, we performed immunohistochemistry for B and T cell antigens and immunoglobulin gene rearrangement by PCR. Of interest, there were no L26+ B cells present in any of the lymph nodes, liver, or bone marrow specimens obtained from the autopsy, although scattered CD3+ T cells were observed. Molecular analysis showed no evidence of the tumor clone in the liver, though a faint signal was found in two of six lymph nodes, suggesting only minimal residual tumor (Fig. 2).

These results also suggest that UCN-01 sensitized normal lymphocytes to the cytotoxic effects of chemotherapy. As shown in Fig. 2, the normal background immunoglobulin “ladder” was present in the patient’s pre-UCN-01/EPOCH biopsy tissues but is absent in all tissues examined at autopsy, indicating loss of normal B cells. Also striking was the lack of recovery of the peripheral lymphocyte compartment after EPOCH, despite a vigorous neutrophil recovery (Fig. 3B). This degree of persistent lymphopenia has not been observed by us in other patients treated with EPOCH chemotherapy and raises the question of whether UCN-01 sensitized a lymphocyte precursor compartment to the effects of chemotherapy. Alternatively, the continued presence of UCN-01 in the patient may have inhibited lymphocyte recovery, though we have not observed chronically depressed lymphocyte counts in other patients treated over prolonged periods with UCN-01 alone. It should be noted that the immunocompromise from the low lymphocyte counts may have contributed to the patient’s death from an opportunistic infection.

An important clinical concept to potentially emerge from this case is that of modulating drug resistance by reducing the “threshold” for apoptosis (2). Experimentally, it is extremely difficult to determine the mechanism of synergy between any two drugs, and this is no less the case with UCN-01 and chemotherapy. Of interest in this regard, experiments by our group in T lymphoblasts suggest that UCN-01 may “independently activate” cdk-1 and cdk-2, leading to abrogation of the G2-M checkpoint (11, 14). Additionally, when the Ca-46 Burkitt’s cell line is irradiated in the presence of low nanomolar concentrations of UCN-01, the cells are unable to arrest at G2 and progress to M phase (29, 30). The authors noted that the loss of the G2-M fraction temporally corresponds with the appearance of DNA fragmentation and suggested that “the G2-M fraction may be a compartment with greater sensitivity to apoptosis.” Others have shown abrogation of the G1 checkpoint by UCN-01, and this too has been associated with a greater sensitivity to induction of apoptosis by DNA-damaging agents (31, 32). These results raise the possibility that the inappropriate activation of cdk by UCN-01 may increase the sensitivity to apoptosis and provide a potential mechanism for modulation of the apoptosis sensitivity threshold by UCN-01.

The results raise several intriguing notions regarding the modulation of clinical drug resistance. Perhaps foremost to be addressed is the relationship of apoptosis “threshold” to clinical drug resistance. If, as we hypothesize, this threshold is an important determinant of chemotherapy sensitivity in lymphomas, then strategies to modulate it may lead to major increases in cell kill that are far greater than can be achieved by dose escalation alone, as suggested by the present case report. However, the identification and development of candidate agents require new paradigms. Preclinically, drug screening methods that use conventional cell death end points will likely overlook agents, which could modulate apoptosis thresholds but do not in themselves cause a significant amount of cytotoxicity. If instead such agents were approached as resistance modulators, then (more appropriately) assays would be based on mechanism of action (e.g., involving apoptosis pathways) or on measures of synergy between the candidate agent and a conventional cytotoxic using an apoptosis end point. It is also important to recognize that, because resistance modulators may not necessarily be clinically active when administered alone, their true effectiveness can only be assessed in combination with a cytotoxic.

For those agents that target broadly expressed proteins/pathways, augmentation of normal tissue toxicity, such as effects on normal hematopoietic compartments caused by simultaneously administered cytotoxic drug(s), should not be unexpected and may require specific supportive measures. Theoretically, this may be overcome by the identification of tumor-specific modulating agents. It is intriguing to hypothesize that monoclonal antibodies such as CD20, which activate apoptotic pathways, may functionally modulate the threshold for chemotherapy-induced apoptosis (33). If, as we hypothesize, the modulation of the apoptosis threshold has the potential to overcome relative drug resistance in hematopoietic neoplasms, the approach could lead to major improvements in clinical outcome.

REFERENCES


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