PEITC in End-Stage B-Cell Prolymphocytic Leukemia: Case Report of Possible Sensitization to Salvage R-CHOP

Arian Nachat, MD; Sam Turoff-Ortmeyer; Chunnan Liu, MD; Michael McCulloch, LAc, MPH, PhD

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ABSTRACT

Introduction: B-cell prolymphocytic leukemia (B-PLL) is a rare, aggressive leukemia distinct from chronic lymphocytic leukemia, with median survival of only 3 years. B-PLL is resistant to most chemotherapy and newer targeted therapies such as alemtuzumab and thalidomide. Phenylethyl isothiocyanate (PEITC) is a natural compound from horseradish with evidence for therapeutic potential in multiple leukemia types.

Case Presentation: Here we present a case report of a 53-year-old man whose chronic lymphocytic leukemia transformed to end-stage B-PLL, disqualifying him for allogenic stem cell transplantation. He was treated with PEITC followed by salvage R-CHOP (Rituximab, Cyclophosphamide, Hydroxydaunorubicin [doxorubicin hydrochloride], Oncovin [vincristine sulfate], Prednisone or Prednisolone) chemotherapy, which led to normalized white blood cell count and disease stabilization that requalified him for allogenic peripheral stem-cell transplant therapy. We conducted a systematic review to analyze and interpret the potential contribution of PEITC to his unexpectedly favorable R-CHOP response. Following sequential 8 weeks of PEITC/pentostatin and 6 cycles of R-CHOP, the patient received allogenic peripheral blood stem cell transplant on an outpatient basis and remains well at the time of this publication, with no evidence of CD20+ small B-cells.

Discussion: Given the limited data for R-CHOP in B-PLL, this patient's recovery suggests presensitization of B-PLL cells toward R-CHOP, potentially justifying further investigation.

BACKGROUND

B-cell prolymphocytic leukemia (B-PLL) is a rare, aggressive lymphoid leukemia with gene expression distinct from that of chronic lymphocytic leukemia.[1] B-PLL is often refractory to chemotherapy, resulting in median survival of only three years.[2] Reports have been published of improved response rates with intravenous alemtuzumab,[2] partial remission with thalidomide,[3] and cure with allogeneic peripheral stem-cell transplantation.[4] In refractory patients, R-CHOP (Rituximab, Cyclophosphamide, Hydroxydaunorubicin [doxorubicin hydrochloride], Oncovin [vincristine sulfate], Prednisone or Prednisolone) is sometimes used as salvage therapy but is seldom successful and prognosis remains poor, with little evidence supporting its clinical use.[5]

Phenylethyl isothiocyanate (PEITC) is a natural compound obtained from horseradish and watercress,[6] with mechanistic and therapeutic evidence for multiple types of leukemia. The antileukemic effect is dose- and time-dependent, acting through multiple tumor suppression signaling pathways: inactivation of protein kinase B (PKB/Akt) and activation of c-Jun N-terminal kinase (JNK) pathways, caspase activation, poly [ADP-ribose] polymerase (PARP) cleavage/degradation, and promotion of apoptosis.[7] PEITC is a biological response modifier, acting as a strong inflammation reducer.[8] Notably, PEITC exhibits tumor cell inhibition properties in fludarabine-resistant chronic lymphocytic leukemia cells obtained from patients, by elevation of reactive oxygen species,[9,10] and by promoting immune response (increasing monocyte macrophage phagocytosis, and increasing natural killer cell cytotoxic activity).[11] A cytotoxic effect on chronic myeloid leukemia cells is achieved through induction of reactive oxygen species (ROS) stress and oxidative damage.[10]

Dietary chemopreventive effects have been identified for PEITC, which works through multiple signaling pathways, at typical human nutritional doses.[12,13] PEITC is one of numerous dietary compounds that work at the epigenetic level: anacardic acid, curcumin, diallyldisulfide, dihydrocoumarin, diindolylmethane, folate, garcinol, genistein and soy isoflavones, indol-3-carbinol, lycopene, nordihydroguaiaretic acid, phenylhexyl isothiocyanate, polyphenols (present in green tea, apples, coffee, chocolate, and raspberries), resveratrol, retinoic acid, selenium, and sulforaphane or PEITC (both of which are from the cruciferous family of vegetables). Metabolic pathways influencing tumor initiation and promotion are also affected by PEITC, through inhibition in human glioma cells of hypoxia-induced HIF-1alpha accumulation and vascular endothelial growth factor expression.[14]

PEITC reverses platinum resistance in lung cancer by inhibiting glutathione-mediated drug efflux,[15] in cisplatin-resistant gastric cancer by suppressing PI3K-PKB/Akt,[16] and in Adriamycin-resistant bladder cancer by blocking PKB/Akt and activating mitogen-activated protein kinase (MAPK) pathways.[17] Additionally, there is synergy of PEITC with

Arian Nachat, MD, is the Physician Lead for Integrative Medicine at Walnut Creek Hospital in CA. E-mail: arian.nachat@kp.org. **Sam Turoff-Ortmeye**r is a Research Associate in Integrative Medicine at Walnut Creek Hospital in CA. E-mail: samturoff@gmail.com. **Chunnan Liu, MD,** is a Medical Oncologist at Walnut Creek Hospital in CA. E-mail: chunnan.liu@kp.org. **Michael McCulloch, LAc, MPH, PhD,** is the Chief of Research for Integrative Medicine at the Pine Street Foundation in San Anselmo and at Walnut Creek Hospital in CA. E-mail: michael.f.mcculloch@kp.org.

Table 1. Tumor cell growth inhibition data

Author, year	Cancer type	Cell type (biopsy/animal/cell culture)	Study type	PEITC Dose	Outcome
Chemoprevention					
Aras et al,[26] 2013	Breast	NMU-induced breast cancer in Sprague Dawley rats	Animal	50-150 µmol/kg, 18 weeks	Chemoprevention of breast cancer via inhibition of angiogenesis, at oral doses reflecting human intake
Sakao et al,[27] 2013	Breast	MDA-MB-231, PC-3, and DU145 cells	Cell culture and animal		PEITC induced apoptosis and inhibited cell migration and viability, via RNA interference of vimentin
Tusskorn et al,[28] 2013	Cholangio-carcinoma		Cell culture		PEITC induced mitochondrial injury and cell death via apoptosis, inhibiting mitochondria and glutathione, but action could be blocked by N-acetylcysteine
Liu et al,[29] 2013	Colon	SW480 epithelial cells	Cell culture		PEITC reduced cell proliferation by upregulating apoptotic signaling
Roy et al,[30] 2013	Colon	Damaged DDB2-deficient colon cancer cells	Cell culture		PEITC demonstrated chemoprevention by inducing apoptosis and senescence, through p38MAPK/JNK pathway and DDB2 activation
Abdull Razis et al,[32] 2014	Mechanistic study	Carcinogen-metabolizing enzymes, in Albino rat	Animal	0.06-6.0 µmol/g for 2 weeks	Modulation of carcinogen-metabolizing enzyme systems: SULT, NAT, UDP, and EH, oral doses reflecting human intake
Palenski et al,[33] 2013	Mechanistic study	Vascular cells	Cell culture		Restored cell phenotype and inhibited angiogenesis, with antioxidant effect and suppression of NF-κB activation
Chen et al,[31] 2013	Oral Cancer	SAS cells	Cell culture		Inhibition of metastatic invasion, via EGFR and related signaling molecules, inhibition of MMP-2 and MMP-9
Direct tumor inhibition					
Lee et al,[34] 2014	Brain	Glioma	Cell culture	(Dose not specified)	Subtoxic levels of PEITC activated TRAIL
Gupta et al,[35] 2013	Brain	Human glioma	Cell culture		Tumor inhibition by suppressing hypoxia-induced accumulation of HIF-1α and VEGF expression
Sarkars et al,[36] 2013	Breast	MCF-7 and MDA-MB-231	Cell culture		PEITC activated apoptosis and suppressed tumor cell growth, by targeting heat shock proteins
Wang et al,[37] 2014	Cervical	Human Cervical HeLa Stem Cells	Cell culture		PEITC induced apoptosis and cell death through the induction of DR4 and DR5 death receptors with Human Cervical HeLa cells along with up regulation of cPARP.
Tsou et al,[38] 2013	Leukemia	WEHI-3 Leukemia BALB/c mice in vivo	Animal (Mice)	IP injection	In both normal and leukemic mice, PEITC stimulated immune response, promoting phagocytosis by PBMC, increasing CD11b, Mac-3, and NK cell cytotoxic activity, and decreasing CD19.
Wang et al,[39] 2014	Leukemia, CML	K562	Cell culture		PEITC is cytotoxic, by inducing ROS stress and oxidative damage
Huang et al,[40] 2014	Melanoma	A375.S2 cells	Cell culture		PEITC caused apoptosis of A375.S2 cells, via ROS-mediated mitochondria-dependent pathways
Jutooru et al,[41] 2014	Pancreatic	(miR-27a)/miR-20a:miR-17-5p	Cell culture		PEITC triggered apoptosis and lessened the growth and spread of pancreatic cancer cells by activation of ROS stress
Stan et al,[42] 2014	Pancreatic	Vitro and MIAPaca2 xenograft animal model	Cell culture	7 µmol/L	PEITC inhibited cell proliferation in-vitro and in-vivo, through down regulation of anti-apoptotic protein, up regulation of proapoptotic protein, and G2/M phase cycle arrest
Inhibition of metastasis					
Gupta et al,[43] 2013	Breast	MDA-MB-231-BR	Animal (Mice)	10 µmol	Reduction in metastasis of breast cancer cells to the brain, and 21% increase in median survival
Li et al,[44] 2013	Prostate	Cell LNCaP tumor	Laboratory - Animal (Mice)	3 µmol/g, oral	PEITC fed to mice slowed tumor growth rates by changing gene expression (up regulation of insulin-like growth factor binding protein 3, fibronectin, thyroxine degradation enzyme, and down regulation of integrin beta 6)

CML = chronic myeloid leukemia; cPARP = poly (ADP-ribose) polymerase cleavage; DDB2 = DNA damage-specific binding protein 2; DNA = deoxyribonucleic acid; DR = death receptor; EGFR = epidermal growth factor receptor; EH = epoxide hydrolase; HIF-1α = hypoxia-inducible factor 1-alpha; IP = intraperitoneal; JNK = c-Jun N-terminal kinase; Mac = macrophage; MAPK = mitogen-activated protein kinase; MMP = matrix metalloproteinase; NAT = N-acetyltransferase; NF-κB = nuclear factor kappa-light-chain-enhancer of activated B cells; NK = natural killer; NMU = N-methyl nitrosourea; PEITC = phenethyl isothiocyanate; PBMC = peripheral blood mononuclear cells; RNA = ribonucleic acid; ROS = reactive oxygen species; SULT = sulfotransferase; TRAIL = tumor necrosis factor-related apoptosis-induced ligand; UDP = glucuronosyl transferase; VEGF = vascular endothelial growth factor.

chemotherapy drugs: with paclitaxel to enhance apoptosis in MCF-7 breast cancer,[18] and with taxol in drug-resistant MCF7 and MDA-MB-231 breast cancer cells by growth inhibition, cell cycle arrest, and apoptosis.[19] In Tables 1 and 2, we concisely summarize the evidence for PEITC: synergism with chemotherapy drugs, direct tumor inhibition, inhibition of metastases, reversal of chemoresistance, and chemoprevention.

However, PEITC has not been reported in mechanistic studies of B-PLL cells or treatment of B-PLL patients. The current case report documents possible pre-sensitization of the patient's B-PLL cells to salvage therapy with R-CHOP, a treatment that typically has poor response in B-PLL patients. This report was prepared in accordance with the CARE (CAse REport) guidelines.[20]

CASE PRESENTATION

Our patient was a 53-year-old man, who was in his usual state of health and good spirits until slow onset of fatigue, dyspnea on exertion, abdominal bloating, night sweats, joint pain, and a 15-lb weight loss from 180 lbs to 165 lbs (Figure 1). Chest radiograph found pneumonia, and palpation revealed no lymph node enlargement but marked splenomegaly. Hematology showed elevated white blood cells (WBC; 157.1 K/μL), low red blood cells (2.94 M/μL), polychromasia 1+, ovalocytes 1+, smudge cells 1+, CD20+ small B-cells with diffuse nodular infiltrate, and CD5+ cells (Figures 2-5; Table 3).

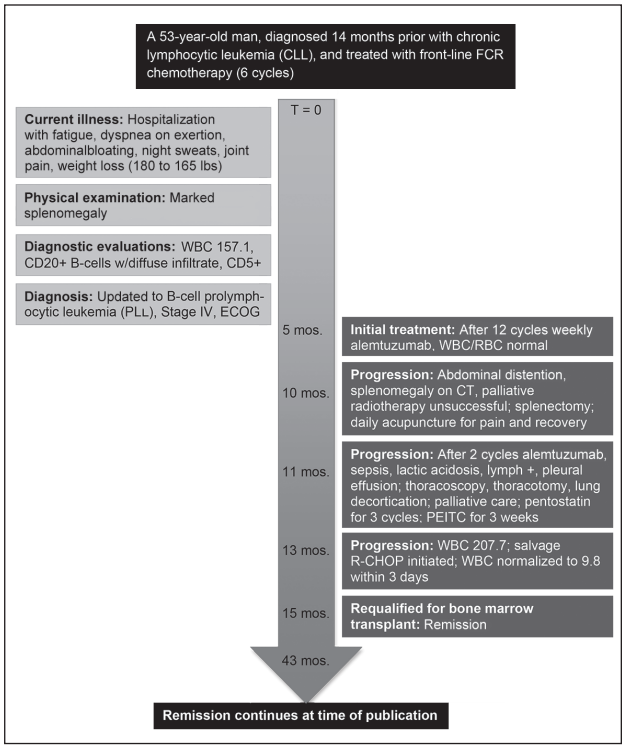

Figure 1. Case Timeline.
CT = computed tomography; ECOG = Eastern Cooperative Oncology Group score; FCR = Fc receptor; mos = months; PEITC = phenylethyl isothiocyanate; RBC = red blood cells; R-CHOP = chemotherapy consisting of rituximab, cyclophosphamide, hydroxydaunorubicin (doxorubicin hydrochloride), Oncovin (vincristine sulfate), prednisone or prednisolone; WBC = white blood cells.

Table 2. Reversal of chemoresistance by PEITC and synergism with chemotherapy drugs

Author, year	Cancer type	Cell type (biopsy/animal/cell culture)	Study type	PEITC dose	Outcome
Reversal of chemoresistance					
Tang et al,[45] 2013	Bladder/ adriamycine	Adriamycin-resistant human bladder carcinoma T24/ADM cells	Cell culture		PEITC reduced doxorubicin resistance by activating MAPK, blocking PKB/Akt, and decreasing expression of multidrug resistant genes and proteins
Gupta et al,[46] 2013	Breast/ taxol	Drug-resistant MCF7 and MDA-MB-231 breast cancer cell lines	Cell culture		Synergism with taxol in growth inhibition, cell cycle arrest, and apoptosis, in drug-resistant MCF7 and MDA-MB-231 breast cancer cells
Tang et al,[47] 2014	Gastric/ cisplatin	SGC7901/DDP cell line	Cell culture		PEITC reduced cell growth and multidrug-resistant genes, via increase in ROS generation and Rhodamine-123, and depletion of glutathione
Yang et al,[48] 2014	Lung/ cisplatin	Non-small cell lung cancer line	Cell culture		Reversal of platinum resistance by inhibiting glutathione-mediated drug efflux
Synergism with chemotherapy drugs					
Halasi et al,[49] 2013	Breast/ bortezomib	Mouse xenograft	Animal		Inhibition of tumor cell growth through combining the FOXM1 inhibitor bortezomib with ROS inducer PEITC
Cang et al,[50] 2014	Breast/ paclitaxel	MCF7 and MDA-MB-231 (MB)	Cell culture		Synergism of PEITC and paclitaxel in apoptotic mechanisms: 1) 6-fold increase in acetylation of alpha-tubulin vs taxol alone; 2) inhibition of cell-cycle regulator Cdk1 and anti-apoptotic protein bcl-2; 3) increase in Bax and PARP protein cleavage
Yang et al,[48] 2014	Lung/ doxorubicin	NCI-H596 NSCLC cell line	Cell culture		40% greater tumor cell growth inhibition by 1:2 molar ratio of CDDP/ PEITC in liposomal form, compared with the same combination in free form

CDDP = cis-diamminedichloroplatinum; FOXM1 = forkhead box M1; MAPK = mitogen-activated protein kinase; PARP = poly (ADP-ribose) polymerase; PEITC = phenethyl isothiocyanate; PKB/Akt = protein kinase B; ROS = reactive oxygen species.

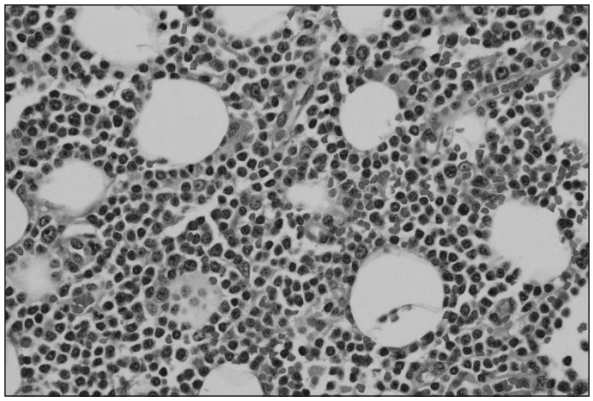

Figure 2. Biopsy specimen of splenic hilar lymph node shows a diffuse proliferation of small lymphoid cells (hematoxylin and eosin stain sample; magnification 400X [239 x 180mm] 72 x 72 DPI).

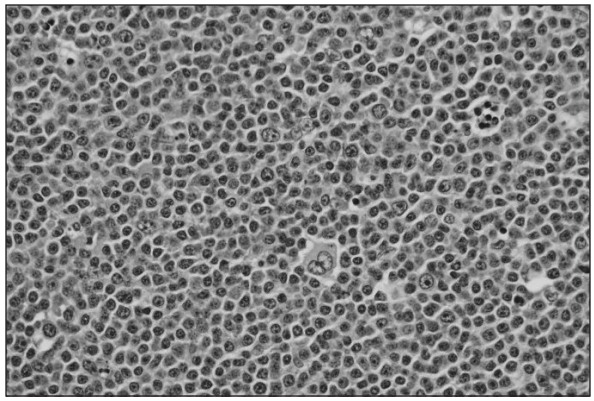

Figure 3. Prolymphocytic leukemia tumor cells extending into splenic perinodal adipose tissue (hematolxylin and eosin stain sample; magnification 400X [239 x 180mm] 72 x 72 DPI).

Planned frontline therapy was 6 cycles of fludarabine-cyclophosphamide-rituximab (FCR) chemotherapy (fludarabine 25 mg/m^2, cyclophosphamide 250 mg/m^2/d, and rituximab 125 mg/m^2 intravenous) and supportive medication (Neupogen, Allopurinol, Bactrim DS, acyclovir, prochlorperazine, and dexamethasone). Disease progression occurred following 2 cycles of FCR, with fever, lower but still elevated WBC (110.7 K/μL), low red blood cells (3.74 M/μL), and increased anisocytosis (2+). On pathology review, the diagnosis was updated to B-PLL, stage IV, with Eastern Cooperative Oncology Group performance score of 2.

Five months after diagnosis of PLL, following 12 cycles of weekly alemtuzumab, there was stabilization of WBC (5.2 K/μL) and red blood cells (4.31 M/μL), but persistent polychromasia (1+) and ovalocytes (1+). Because the patient had 2 siblings, planning and evaluation for allogenic bone marrow transplant was initiated.

Ten months after diagnosis, the patient reported profound fatigue, blurred vision, pressure behind his eyes, spontaneous unprovoked perspiration, and abdominal distention with early satiety. Palpation revealed extensive splenomegaly across the midline to the right midclavicular line, confirmed by computed

Table 3. Serology data by clinical treatment event

Clinical events timeline	Baseline	2 months After 2 cycles of FCR, stopped due to progression	5 months After 12 cycles of weekly alemtuzumab	11 months After splenectomy, because of progression after 2 doses of alemtuzumab, started PEITC	12 months Continued disease progression, before R-CHOP	13 months After first cycle of R-CHOP	19 months 4 months after BMT, no evidence of CLL or PLL
WBC (K/μL)	157.1	110.7	5.2	73.4	207.7	9.8	4.5
RBC (M/μL)	2.94	3.74	4.31	2.72	2.67	2.60	2.75
Hemoglobin (g/dL)	8.0	11.2	13.5	8.2	8.3	7.9	9.3
Hematocrit (%)	24.8	34.0	39.3	25.3	24.4	22.9	28.1
RDW (%)	17.1	22.7	14.5	16.3	21.4	20.9	20.1
Platelet (K/μL)	104	61	106	341	129	133	124
Segmented neutrophils (%)	5	4	77	32		88	
Lymphocytes (%)	91	95	11	92	79	3	11.7
Anisocytosis	1+	2+			1+	1+	
Monocytes (%)		1	11		2	1	0.7
Target Cells					1+	1+	
LDH			214				
Polychromasia	1+	1+	1+				
Ovalocytes	1+		1+			1+	
Smudge Cells	1+						
CD20+ small B-cells	Present	Diffuse nodular infiltrate					No evidence

BMT = bone marrow transplantation; CLL = chronic lymphocytic leukemia; FCR = chemotherapy with fludarabine, cyclophosphamide, and rituximab; K = thousand; LDH = lactate dehydrogenase; M = million; PEITC = phenethyl isothiocyanate; PLL = prolymphocytic leukemia; RBC = red blood cells; R-CHOP = chemotherapy with rituximab, cyclophosphamide, hydroxydaunorubicin (doxorubicin hydrochloride), Oncovin (vincristine sulfate), prednisone or prednisolone; RDW = red blood cell distribution width; WBC = white blood cells.

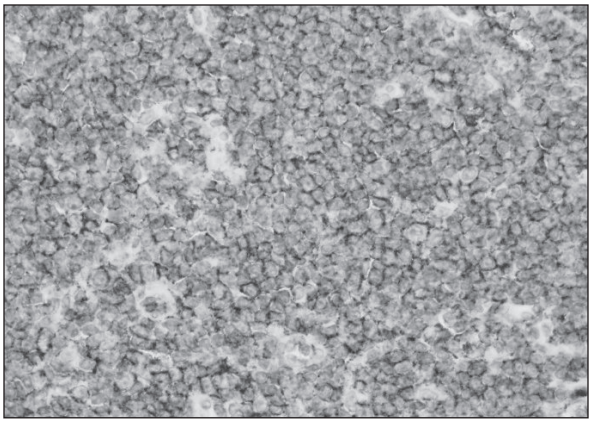

Figure 4. CD20 showing membrane positivity (immunohistochemical stain; magnification 400X [239 x 180mm] 72 x 72 DPI).

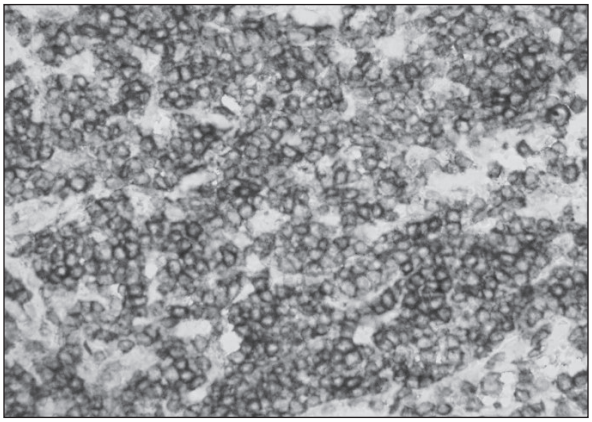

Figure 5. CD5 showing strong, diffuse positivity (immunohistochemical stain; magnification 400X [239 x 180mm] 72 x 72 DPI).

tomography (Figure 6). Three treatments of palliative radiation therapy were unsuccessful, therefore splenectomy was performed. Following surgery, the patient developed protein energy malnutrition, sinus tachycardia, bilateral pleural effusion, cholelithiasis, dyspnea, and portal vein thrombosis. For treatment of his significant pain, the patient was referred to the integrative pain management service for acupuncture (daily during this and following hospital admissions).

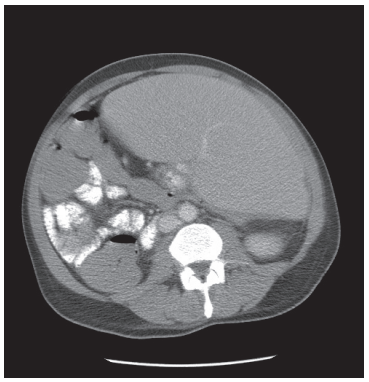

Figure 6. Computed tomography scan of extensive splenomegaly (135 x 135mm [96 x 96 DPI]).

Eleven months after diagnosis, despite 2 cycles of alemtuzumab with palliative intent, there was further disease progression. The patient was readmitted for sepsis with fever, lactic acidosis (4.9 mmol/L), worsening serology, and atypical lymph at 92% (Table 1). Because of significant pleural effusion, the patient underwent transpleural thoracoscopy, exploratory thoracotomy, and lung decortication. Given the patient's deteriorating status, bone marrow transplantation was canceled and a palliative care team was assigned to his case.

Adjunctive oral PEITC was introduced, with the patient being eligible on the basis of published evidence for disease-modifying potential, and lack of evidence for herb-drug interactions. PEITC was provided to the patient on a compassionate use basis because there were no treatment options left available to him. Two weeks after PEITC was initiated, the patient's oncologist added pentostatin to his alemtuzumab, given the alemtuzumab's poor potential for success.

PEITC was provided by KW Botanicals (San Anselmo, CA) as a 1:1 watercress fluid extract of the fresh leaf, prepared from cloned *Nasturtium officinalis* using corn alcohol, with plant identity verified by a botanist, using organoleptic methodology and microscopy. Daily oral dose of the extract was 2 mL, corresponding to an approximate daily dose of PEITC of 1 mg, for a duration of 3 weeks. Following introduction of PEITC, the patient's symptoms continued to improve, but WBC remained abnormal.

Twelve months after diagnosis, there was continued disease progression, with a new left neck mass, night sweats, chills without fever, and elevation of WBC to 207.7 K/μL. Examination revealed a 5 cm, tender mass. Computed tomography showed extensive left cervical adenopathy. Treatment was changed to salvage R-CHOP (3 cycles, every 3 weeks), and PEITC discontinued one week before starting R-CHOP. The patient's response to sequential 8 weeks of PEITC/pentostatin, followed by 6 cycles of R-CHOP, was substantial, with normalization of WBC within 2 days (from 150K/μL to 9.8 K/μL). R-CHOP was continued for 6 cycles, leading to discharge from the palliative care team.

Fifteen months after initial diagnosis, and following this course of sequential 8 weeks of PEITC/pentostatin and then 6 cycles of R-CHOP, the patient received allogenic peripheral blood stem cell transplant on an outpatient basis at Stanford University Hospital in Stanford, CA, and was followed up for 90 days after the transplant. Posttreatment bone marrow biopsy was normal; neck lesions and chest and left pelvic lymphadenopathy resolved, with only mild residual fluorodexyglucose (FDG) uptake. Other previously noted lesions in both lung bases appeared stable in size and FDG uptake. The patient was declared to be in remission.

Forty-three months after initial diagnosis, the patient's remission continues. Other than one episode of neutropenic fever and chronic mild to moderate graft-versus-host disease, the patient remains well to this day, with no evidence of CD20+ small B-cells.

DISCUSSION

PEITC exhibits synergism with numerous chemotherapy drugs,[18,21,22] including doxorubicin, which is a component of R-CHOP.[23] We were not able to identify published evidence for synergism of PEITC with pentostatin. Researchers have

also shown that PEITC has direct and significant oxidative cytotoxic activity against other leukemia cells—with low toxicity to normal lymphocytes—such as chronic lymphocytic leukemia cells obtained from patients whose disease was resistant to fludarabine chemotherapy.[9] Cells from those patients were eliminated by PEITC.

At present, it is known that one way in which PEITC accomplishes this sensitization of cancer cells to chemotherapy is by depleting the cancer cells of tubulin, a normally stable cell structure protein required in the process of cell cycle progression.[24] It has also been found that this degradation of tubulin by PEITC is an irreversible process,[25] suggesting there is biological plausibility for our patient's PLL tumor cells to continue to exhibit enhanced vulnerability for some time after PEITC exposure. Taken together, these data support our hypothesis that this patient's chemoresistant B-PLL cells were sensitized to favorable response to R-CHOP, a drug not expected to have been so successful in his end-stage condition.[5] This favorable response enabled him to requalify for life-saving allogenic peripheral blood stem cell transplant.

PEITC exhibits chemopreventive effects in the following cancer cell lines and animal models: breast,[26,27] cholangiocarcinoma,[28] colon,[29,30] and oral (squamous).[31] These effects are mediated via numerous pathways and mechanisms: anti-angiogenesis,[26] induction of apoptosis,[27,28,30] inhibition of EGFR, MMP-2 and MMP-9,[31] modulation of carcinogen-metabolizing systems,[32] and NF-κB suppression.[33] In the animal model studies, these effects were seen at oral doses reflecting human dietary intake of PEITC-containing foods.[26,32] PEITC additionally accomplishes direct tumor cell inhibition, in the following cell lines and animal models: brain (glioma),[34,35] breast,[36] cervical,[37] leukemia,[38,39] melanoma,[40] and pancreatic.[41,42] Two recent studies also suggest PEITC has metastatis inhibition capabilities in breast[43] and prostate[44] cancers (Table 1).

Promising chemotherapy-specific effects have been described for PEITC: reversal of chemoresistance data exist for bladder cancer and adriamycin,[45] breast cancer and taxol,[46] gastric cancer and multidrug resistance gene,[47] lung cancer and cisplatin[48] (Table 2). Synergism with specific chemotherapy agents in defined cancers has been reported for bortezomib[49] and paclitaxel[50] in breast cancer, and cisplatin in lung cancer.[48]

This case report provides justification of in vitro PEITC-drug synergy testing, which if successful would be a step toward in vivo and phase I combination therapy trials. ❖

Disclosure Statement

The author(s) have no conflicts of interest to disclose.

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All Things to All Tissues

We, therefore, worked on the principle that blood is all things to all tissues, being meat to the hungry, blood to the malarious, and life-giving fluid to the collapsed and to those losing protein by the discharge of albuminous exudates.

— Jacob Markowitz, MBE, MD, PhD, MS, 1901-1969, Canadian physician, pioneer in experiemental surgery, and war hero