

Complete response to azacitidine priming and nab-paclitaxel in non-Hodgkin lymphoma resistant to biochemotherapy

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Abstract. The standard of care for first-line therapy in diffuse large B-cell lymphoma (DLBCL) is the rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP) regimen. For patients who fail to respond, have an incomplete response or relapse, numerous effective options exist besides salvage cisplatin-based regimen and autologous stem cell therapy. Even with this approach, the outcome remains very poor for this group of patients. The present case illustrates a 55-year-old woman diagnosed with DLBCL, who experienced an early incomplete response, later progression during treatment with the R-CHOP regimen. The patient received salvage therapy with rituximab, cisplatin and gemcitabine, again with an incomplete response. The patient declined consideration for stem cell therapy. Her disease progressed and she enrolled in the present phase I trial using azacitidine priming and nano-albumin-bound (nab)-paclitaxel. After three cycles, follow-up positron emission tomography/computed tomography revealed a complete response for the first time since her initial diagnosis and the patient has remained disease-free for >6 years. Azacitidine and nab-paclitaxel combination appeared to be an effective regimen for the treatment of this patient with refractory DLBCL.

Introduction

Non-Hodgkin lymphoma (NHL) is the fifth most common cancer type in the USA at 7 cases per 100,000 individuals per year, and is the sixth leading cause of cancer-associated mortality in both men and women (1). Diffuse large B-cell lymphoma (DLBCL) accounts for ~25% of all NHL cases and is an aggressive lymphoma with patients only having months to live

without treatment (2). The first-line chemotherapy for the treatment of DLBCL is rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP). While improvements in first-line therapy have resulted in 67% of patients with DLBCL being in a disease-free state 4 years following diagnosis, one-third of patients with DLBCL will have disease that is refractory to initial R-CHOP (<50% decrease in tumor burden) or have a recurrence of their cancer after achieving complete remission (3). Due to the substantial number of patients who have refractory DLBCL, numerous second-line chemotherapy regimens have been developed for the treatment of DLBCL; however, the complete response (CR) rate for these regimens is poor, ranging between 16 and 62% (Table I) (4-8). Additionally, a number of the second-line regimens for refractory DLBCL have significant side effect profiles (Table I); therefore, novel treatment approaches are required. The present study reported a case of refractory DLBCL treated with a novel chemotherapeutic regimen, azacitidine priming followed by nanoparticle albumin-bound (nab)-paclitaxel, that may have promise as a second-line treatment for refractory DLBCL.

Case report

A 55-year-old Caucasian female initially presented to the Mitchell Cancer Institute (Mobile, AL, USA) in September 2006 with B-symptoms of night sweats, a 40 pound weight loss and abdominal pain. Initial computed tomography (CT) of her abdomen revealed a 7x7.3 cm size periaortic mass, multiple enlarged periaortic lymph nodes and a right upper quadrant node measuring 1.8x2.6 cm. A biopsy was performed and the patient was found to have a centroblastic variant of stage IIIB DLBCL. The patient's age adjusted International Prognostic Index (IPI) score was 3, due to an elevated lactate dehydrogenase at 307 and her stage IIIB disease. Her age adjusted IPI of 3 placed her at high risk with a 32% 5-year survival. The patient was treated with 8 cycles of R-CHOP; however, a positron emission tomography (PET)-CT at the completion of her therapy in May 2007 revealed residual disease in her mediastinum and periaortic region. The patient continued to have an excellent performance status (PS) and proceeded with 8 cycles of second-line therapy with gemcitabine, cisplatin, and rituximab. After 8 cycles, a PET-CT revealed a partial response in November 2007. The patient was evaluated for

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Table I. Summary of phase I/II clinical trials for second-line therapies in the treatment of DLBCL.

Author, year	No. patients	Therapy	Response rate and toxicities	Refs.
Kewalramani <i>et al</i> , 2004	36 recurrent or refractory DLBCL	RICE	53% CR. Grade III/IV febrile neutropenia (7.5%)	(4)
Mey <i>et al</i> , 2006	53 recurrent or refractory aggressive B Cell NHL	DHAP+R	62% RR. Grade III/IV (79%) hematological toxicity, grade III febrile neutropenia (4%)	(5)
Crump <i>et al</i> , 2004	51 recurrent or refractory DLBCL	GDP	16% CR, 33% PR. Grade III/IV neutropenia (72%), thrombocytopenia (28%)	(6)
Velasquez <i>et al</i> , 1994	122 recurrent or refractory adult lymphoma	ESHAP	37% CR, 27% PR. Febrile neutropenia (30%) and treatment related mortality (6%)	(7)
López <i>et al</i> , 2008	32 recurrent or refractory DLBCL	GemOx	34% CR, 43% RR. Grade III/IV hematologic (43%) and neurotoxicity (7%)	(8)

RR was calculated as PR+CR. RICE, rituximab, ifosfamide, carboplatin and etoposide; DHAP+R, dexamethasone, cisplatin and cytarabine, plus rituximab; GDP, gemcitabine, dexamethasone and cisplatin; ESHAP, etoposide, methylprednisolone, cytarabine and cisplatin; GemOx, gemcitabine and oxaliplatin; CR, complete remission; PR, partial remission; RR, response rate; NHL, non-Hodgkin lymphoma; DLBCL, diffuse large B-cell lymphoma.

autologous hematopoietic cell transplant (HCT), but declined this option. The patient continued rituximab alone until April 2008 when a PET-CT revealed a progressive disease.

At that time, the patient still exhibited an excellent PS of 0 and elected to enroll in a phase I clinical trial of azacitidine priming and nab-paclitaxel for the treatment of advanced or metastatic solid tumors (Clinical trial no. NCT00748553). The patient received treatment with azacitidine at 75 mg/m² subcutaneously, daily from days 1 through 5, followed by nab-paclitaxel at 100 mg/m² intravenously on days 8, 15 and 22, of each 28-day cycle for a total of 6 cycles. Most adverse events were grade I and II, with one grade III event (neutropenia) during cycle five. Two doses of nab-paclitaxel were withheld as a result of a grade II bronchiolitis during cycle four and the grade III neutropenia during cycle five. After cycle three, a PET-CT revealed no evidence of the disease. At >6 years since the patient first received study treatment, subsequent scans continued to show a CR with no evidence of disease recurrence. The patient experienced very few adverse events during and after treatment.

Discussion

The low CR rates observed among the numerous second-line therapies currently used for refractory DLBCL, coupled with the significant number of patients with DLBCL who are refractory to initial R-CHOP therapy, highlights the requirement for novel approaches to second-line therapy for DLBCL. Second-line therapies in refractory DLBCL are often used to attain a CR or partial remission, in order to get a patient to an autologous HCT. Second-line therapies often have significant toxicity profiles that reduce their tolerability, and when combined with their low response rates, limit the number of patients who can make it to autologous HCT (Table I). Also, numerous elderly patients and those with significant

co-morbidities cannot tolerate autologous HCT (9). For these patients, a second-line therapy that can achieve a durable CR, independent of autologous HCT, with a tolerable side effect profile would be of great utility. The present study introduces a novel salvage regimen for the treatment of refractory DLBCL, azacitidine priming followed by nab-paclitaxel, that achieved a CR that has persisted for >6 years.

Taxanes have been tested in several trials to treat relapsed or refractory lymphomas (10-13). When used as a single agent in this patient population, paclitaxel had a response rate of 17-25% (10-12). Although, a recent pre-clinical study indicated that doxorubicin-resistant lymphoma may be particularly sensitive to taxanes (14). Nab-paclitaxel is unique in that the nanoalbumin particle activates Gp60 albumin-specific receptors on the cell walls of endothelial cells. These receptors in turn activate caveolin-1, which opens cell walls via caveolae, allowing nab-paclitaxel to enter the tumor interstitium (15,16). Tumor cells release a specific protein (SPARC) that binds albumin, thus capturing nab-paclitaxel and increasing intratumoral concentrations to higher levels than observed with conventional single agent paclitaxel (17).

SPARC is a secreted glycoprotein that has been found to have a high affinity for binding albumin (18). When the promoter region of SPARC undergoes hypermethylation, it results in decreased protein expression of the SPARC. Hypermethylation of the SPARC promoter region has been noted in colorectal, pancreatic, lung and ovarian cancer types, along with decreased protein expression of the SPARC (19-22). In these cancer cells, increased expression of SPARC was accomplished through the use of a hypomethylating agent. Therefore, priming of a malignancy with a hypomethylating agent, including azacitidine, can result in increased concentrations of cytotoxic nab-paclitaxel in tumor cells. A recent pre-clinical and phase I study by Clozel *et al* (23), subsequent

to the completion our phase I clinical trial, confirmed that priming with a hypomethylating agent prior to use of cytotoxic chemotherapy regimens increases the chemosensitivity of DLBCL. Clozel *et al* (23) demonstrated reversal of doxorubicin resistance in lymphoma cells *in vitro* and *in vivo* using DNA demethylating agents, and then performed a phase I trial using azacitidine priming prior to R-CHOP therapy for first-line treatment of newly diagnosed lymphoma patients and reported a CR in 11/12 patients.

The present study is the first, to the best of our knowledge, reported use of azacitidine priming followed by nab-paclitaxel to achieve a durable CR in refractory DLBCL. Nab-paclitaxel and azacitidine appeared to have a synergistic effect in increasing the concentration of paclitaxel in tumor cells. In the future, a clinical trial is required to further investigate the potential of nab-paclitaxel and azacitidine as a novel second-line agent for refractory DLBCL that includes the addition of an anti-CD20 agent; for example rituximab. The addition of rituximab to first and second-line therapies, particularly in those without prior exposure to rituximab, has significantly improved outcomes (24).

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