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Modified Outpatient Dexamethazone, Cytarabine and Cisplatin Regimen May Lead to High Response Rates and Low Toxicity in Lymphoma

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Key Words
Dexamethasone, cytarabine and cisplatin · Non-Hodgkin's lymphoma · Hodgkin's disease · Salvage chemotherapy

Abstract
Objective: Our purpose was to investigate the efficacy of and establish a toxicity profile for a modified regimen of dexamethasone, cytarabine and cisplatin (DHAP) for lymphoma outpatients. ***Subjects and Methods:*** Fifty-one lymphoma patients, 26 with Hodgkin's disease and 25 with non-Hodgkin's lymphoma, were included. The patients' median age was 32 years (range: 17–61). Twenty had progressive/refractory disease and 31 relapsed disease. Twenty-five were in clinical stage I/II and 26 in clinical stage III/IV before the initiation of salvage chemotherapy. DHAP consisted of dexamethasone (40 mg i.v. on days 1–4), cytarabine (2 g/m^2 i.v. as 3-hour infusion on days 2 in the evening and 3 in the morning) and cisplatin (35 mg/m^2 as 2-hour infusion on days 1–3) were administered every 21 days. A total of 154 cycles of modified DHAP were administered, with a median of 3 cycles per patient (range: 2–4). ***Results:*** The main toxicity was myelosuppression. WHO grade III–IV neutropenia and grade III–IV thrombocytopenia were observed in 27 (52.9%) and 21 (41%) patients, respectively. The overall response rate (85% for Hodgkin's disease and 95% for non-Hodgkin's lymphoma) was 88.3% (39.2% complete response and 49.1% partial response). ***Conclusion:*** The results showed that this outpatient schedule of DHAP was well tolerated and an effective salvage regimen.

Introduction

Patients with relapsed or refractory Hodgkin's disease (HD) and non-Hodgkin's lymphoma (NHL) generally have a poor prognosis. The optimal salvage chemotherapy regimen for these patients remains unclear, due to the lack of randomized trials comparing the efficacy of different conventional salvage chemotherapies or the heterogeneous patient population in published studies [1, 2] and the small number of enrolled patients.

A regimen combining dexamethasone, cytarabine and cisplatin (DHAP) is one of the most widely used and effective salvage regimens for relapsed or refractory NHL [3]. Overall response rates of approximately 50–60% have been reported for NHL patients treated with DHAP [3, 4]. However, available data regarding the effectiveness of this regimen as salvage therapy for patients with HD are relatively limited [5]. The conventional DHAP regimen requires hospitalization of patients, a disadvantage of this

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regimen. We therefore designed a phase II study to investigate toxicity and the efficacy of an outpatient schedule of a regimen of DHAP in patients with relapsed or refractory HD and NHL.

Subjects and Methods

Fifty-one consecutive patients with relapsed or refractory lymphoma were treated with a modified DHAP salvage regimen at our institution. Of these, 25 were NHL and 26 HD. The histologies were as follows: nodular sclerosing (50%), mixed cellular (15%), lymphocyte predominant (35%) for HD and diffuse large B cell (100%). None of the patients had T cell histologies. The median age of the patients was 32 years (range: 17–61). Forty-one patients were male and 10 were female. Twenty patients had progressive/refractory disease, and 31 patients had relapsed disease. Twenty-six patients were in clinical stage III/IV and 25 in clinical stage I/II before the initiation of salvage chemotherapy. B symptoms were present in 15 patients.

The initial chemotherapy regimen for NHL patients was CHOP (21 patients), CHOP-bleomycin (3 patients) or M-BACOD (1 patient). On the other hand, HD patients had been treated with ABVD (14 patients) and ABVD/MOPP (12 patients). The median number of previous chemotherapy cycles for all patients with HD and NHL was 7 (range: 3–12). Twenty-one patients had been treated with combined chemoradiotherapy during the first-line treatment.

A total of 154 cycles of modified DHAP were administered on a full dose, with a median of 3 cycles per patient (range: 3–4). Only 1 patient received 4 cycles without necessitating a dose reduction. Although the drugs were given at full dose, the treatment was well tolerated by all patients. The eligibility criteria were as follows: age <70 years, histopathologically proven diagnosis of relapsed or refractory NHL or HD, Eastern Cooperative Oncology Group performance status <3, normal renal (serum creatinine level ≤2.0 mg/dl or creatinine clearance ≥60 ml/min), hepatic (total bilirubin levels within reference ranges, alkaline phosphatase level ≤5 times the upper limit of normal and serum transaminase ≤1.5 times the upper limit of normal), pulmonary and cardiac function, a life expectancy of >3 months, absolute neutrophil count ≥1,500/mm^3 and platelet count ≥100,000/mm^3. Patients were excluded if one of the following findings were present: central nervous system involvement, human immunodeficiency virus infection, active infection or a formal contraindication to APBSCT. Patients with mantle cell, Burkitt's or lymphoblastic lymphoma and small lymphocytic lymphoma or follicular lymphoma (grade I–II) were also excluded.

Before DHAP salvage chemotherapy, all patients underwent staging procedures by performing chest X-ray, computed tomography scans of cervical, chest, abdominal and pelvic regions, and bone marrow biopsy. Positron emission tomography scans were optional. The salvage regimen consisted of dexamethasone (40 mg i.v. in 250 ml 0.9% NaCl in half an hour on days 1–4), cytarabine (2 g/m^2 i.v. as 3-hour infusion on day 2 in the evening and day 3 in the morning) and cisplatin (35 mg/m^2 i.v. as 2-hour infusion in 1,000 ml Isolyte S on days 1–3). This regimen was administered every 3 weeks to outpatients using routine parenteral antiemetic prophylaxis (5-HT$_3$ receptor antagonist (granisetron 2 mg or tropisetron 5 mg), ranitidine 25 mg, feniramine maleate 45.5 mg) and intravenous hydration (1,000 ml 0.9% NaCl was administered 1 h before and after cisplatin administration). Patients were closely followed for infectious, hematological and nonhematological toxicities during the chemotherapy cycle periods. The toxicity profile was evaluated using the World Health Organization (WHO) toxicity grading scale.

Primary progressive/refractory disease was defined as disease progression during the front-line chemotherapy. A transient complete response (CR) or partial response (PR) lasted <3 months after induction treatment. Progressive disease was defined as ≥25% increase in the greatest diameter of any previously identified abnormal lesion for partial responders or nonresponders and the appearance of any new lesion within 3 months after the end of therapy. Relapsed disease was defined as disease progression after CR lasting >3 months.

Results

The characteristics of the patients treated with the DHAP regimen are given in table 1. The major toxicity was myelosuppression (table 2). WHO grade III–IV neutropenia and grade III–IV thrombocytopenia were observed in 27 (52.9%) and 21 (41%) patients, respectively. Febrile neutropenia requiring hospitalization developed in 11 (21.5%) patients and lasted a mean of 5 days (range: 3–7). Although WHO grade III or IV neurotoxicity or renal toxicity was not encountered in our patients, grade I or II neurotoxicity and transient renal toxicity were observed in 7 (13.7%) and 4 (7.8%) patients, respectively (table 2). Patients who did not achieve a long-lasting response rate died due to the progression of their disease. No death attributable to DHAP chemotherapy or transplantation was observed.

The overall response rate was 88.3%; 39.2% CR and 49.1% PR; for NHL: 92% (23/25) and HD: 85% (22/26). Six patients (2 NHL, 4 HD) were refractory to the modified DHAP regimen (table 3). The details concerning the clinical response in the NHL and HD patients are shown in table 3. The median progression-free survival was 10.5 months (95% CI: 6.8–14.0), and the median overall survival was 28 months (95% CI: 16.8–50.6).

Discussion

The relatively high overall response rates of 88.3% and CR rate of 39.2% obtained in our study demonstrated that this outpatient-based schedule of DHAP may be a promising and feasible salvage therapy for lymphoma patients. Our response rates seemed to be comparable or slightly

Table 1. Characteristics of the patients treated with the modified dexamethasone, cytarabine and cisplatin regimen

Characteristics	Number	Percent
Patients	51	
Median age, years	32 (range: 17–61)	
Male	41	80.4
Female	10	19.6
Diagnosis		
NHL	25	49.1
HD	26	50.9
Performance status		
0	10	19.6
1	31	60.8
2	10	19.6
Median number of previous chemotherapy cycles	7 (range: 3–12)	
Pre-DHAP disease status		
Relapse	31	60.8
Progressive/refractory	20	39.2

Table 2. WHO Grade III–IV toxicity profile of the modified DHAP regimen

Toxicities	NHL (n = 25)	HD (n = 26)	Total (n = 51)
Neutropenia	15 (60)	12 (46)	27 (52.9)
Febrile neutropenia	6 (24)	5 (19)	11 (21.5)
Thrombocytopenia	11 (44)	10 (38.4)	21 (41)
Anemia	7 (28)	7 (26.9)	14 (27.4)
Nausea/vomiting	5 (20)	5 (19.2)	10 (19.6)
Neurotoxicity	0	0	0
Renal toxicity	0	0	0

Figures in parentheses are percentages.

superior to the other reported studies using a variety of salvage chemotherapy regimens such as DHAP, ICE (ifosfamide, carboplatin and etoposide) or IIVP (ifosfamide, idarubicin and etoposide) [3, 6–9]. This favorable outcome may be linked to some demographic features of our patients. Firstly, the median age was 32, representing mostly younger patients. Secondly, at study entry, most patients (80.4%) had a good performance status (Eastern Cooperative Oncology Group 0 or 1), and symptoms were present in only 15 (29.4%) patients. Finally, 25 (49%) patients had stage I–II disease, and only 20 (39.2%) patients had progressive/refractory disease.

DHAP regimen is used relatively less frequently as salvage chemotherapy in patients with HD. The overall response rates to DHAP in patients with HD of 85% and CR of 42% are comparable to those of a recent study investigating the effectiveness of time-intensified DHAP in relapsed and refractory HD, supported by G-CSF [9]. The authors determined the remission status (relapsed versus progressive HD) and the stage at relapse (stage I/II vs. stage III/IV) as significant factors in response to DHAP. Although the number of patients with HD who received modified DHAP in our study was relatively small, our response rates seemed to be slightly higher than those reported in other studies using modified DHAP regimens adding doxorubicin (ASHAP; Adriamycin = doxorubicin, Solu-Medrol = methylprednisolone, high-dose Ara-C = cytosine arabinoside, platinum = cisplatinum) or epirubicin (ESHAP) in patients with HD [10, 11].

Based on our current study, we can speculate that the modified DHAP regimen was well tolerated by the patients. The major treatment-related toxicity was hematologic toxicity. Only 21.5% of the patients required hospitalization because of febrile neutropenia. However, none of them encountered a life-threatening infection and all

Table 3. Response of lymphoma patients to the modified DHAP regimen

	OR	CR	PR	Nonresponders
All patients (n = 51)	45 (88.3)	20 (39.2)	25 (49.1)	6 (12%)
NHL patients (n = 25)	23 (92)	9 (36)	14 (56)	2 (8%)
HD patients (n = 26)	22 (85)	11 (42)	11 (42)	4 (15%)
Patients with progressive/ refractory disease (n = 20; 10 NHL, 10 HD patients)	14 (70) (8 NHL, 6 HD)	0 (0)	14 (70)	6 (30%)

Figures are numbers of cases with percentages in parentheses. OR = Overall response.

had a complete recovery after empirical use of wide-spectrum antibiotics. No grade III or IV neurotoxicity and renal toxicity were seen, and grade I or II transient renal toxicity were observed in only 7.8% of the patients. This favorable toxicity profile of the current study may have been related to modification of the DHAP schedule: cisplatin was given on 3 consecutive days and cytarabine was given on 2 consecutive days. Velasquez et al. [3], who first used conventional DHAP in lymphoma patients, reported that 48% of the patients required hospitalization for management of febrile neutropenia and 10 died of septic complications. Additionally, they observed a treatment-related renal insufficiency in 20% of the patients, which was permanent in 6.6%.

Conclusion

Preliminary results of the current study indicated that modified DHAP seemed to be an effective and feasible therapeutic alternative salvage regimen for patients with relapsed or refractory HD and NHL. Modification of the conventional DHAP regimen allowed a reduction in the treatment-related toxicity and maintained a good antineoplastic efficacy. Another significant advantage of this regimen is the feasibility of chemotherapy on an outpatient basis.

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