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Gemcitabine, vinorelbine and dexamethasone: A safe and effective regimen for treatment of relapsed/refractory hodgkin's lymphoma

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ABSTRACT

Background: Salvage regimens in relapsed/refractory Hodgkin's lymphoma (HL) differ in their efficacy and toxicity profiles. Gemcitabine (G), vinorelbine (V) and liposomal doxorubicin (GVDoxil) is one regimen with high response rates but has high toxicity and cost. We devised a regimen of GVDex by substituting the more expensive liposomal doxorubicin with the cheaper high-dose dexamethasone (Dex).

Patients and methods: We analyzed the data of 48 adult and paediatric patients of relapsed/refractory HL who received GVDex as salvage therapy. GVDex was delivered as outpatient once in 3 weeks (Q3 weekly) (G 1000 mg/m^2 IV over 30 min on D1, 8; V 25 mg/m^2 IV fast infusion on D1, 8; Dex40 mg PO D1-4) for 2–3 cycles. We present the overall response rate, toxicity, progression-free (PFS) and overall survival (OS) from the time of start of GVDex.

Results: Forty-eight patients [median age: 24 years (5–63)] received GVDex [(median cycles:3(1–6)] in this period. Median time from diagnosis to the first relapse was 18.9 (2–119) months. Overall response rate [ORR = complete (CR) + partial (PR)] was 63%. Eleven (23%) patients developed febrile neutropenia. After a median follow-up of 20 months, the Kaplan-Meier estimates of patients alive and progression-free at 24 months were 60% and 49%, respectively.

Conclusions: The response rates with GVDex were comparable to those reported with GVDoxil when used as a first-line salvage regimen in relapsed/refractory HL. It was an effective regimen even in patients who failed 2 lines of therapy for HL.

1. Introduction

The majority (70–80%) of patients diagnosed with Hodgkin's lymphoma (HL) are cured with primary therapy [1,2]. About 20–30% of them are either refractory or relapse after initial complete response and require salvage therapy. Treatment of relapsed/refractory HL (R/R HL) involves salvage chemotherapy followed by high-dose therapy (HDT) and autologous stem cell transplantation (ASCT) [2]. Salvage chemotherapy aims to induce a second response [partial (PR) or complete response (CR)] prior to the procedure of HDT/ASCT. Successful salvage regimens serve to establish sensitivity of the lymphoma to chemotherapy, an important predictor of outcomes after HDT. Achievement of complete metabolic response prior to transplant has been shown to be a very robust prognostic factor [3–5]. A number of salvage regimens exist for the treatment of R/R HL [2]. Gemcitabine-based regimens have shown activity in salvage therapy of lymphomas and may be less toxic than older regimens like DHAP (dexamethasone, cytarabine and cisplatin), or ICE (ifosfamide, carboplatin and etoposide) (6). A randomized trial in relapsed non-hodgkin's lymphoma (NHL) had shown that the gemcitabine-based regimen gemcitabine, cisplatin and dexamethasone (GDP) was equally effective and significantly less toxic than DHAP [7]. Similar randomised trials comparing salvage regimens are lacking in HL, hence individual regimens are compared across separate clinical trials [8–12]. One of the highest

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responses (ORR 70–80%) reported is with a combination of gemcitabine, vinorelbine and liposomal doxorubicin (GVDoxil) [8,12,13]. However, the toxicity of this combination was high with almost two-thirds of patients developing febrile neutropenia [8]. Moreover, liposomal doxorubicin is expensive and increases the cost of delivering this regimen. Recently, combinations of antibody-drug conjugate (Brentuximab vedotin) and checkpoint inhibitor (nivolumab) or chemotherapy (bendamustine) have yielded very high responses in R/R HL (90–93%) [14,15]. However, these are expensive and remain inaccessible for the majority of patients in India and developing countries in the world. Hence conventional chemotherapy salvage regimens remain relevant in many parts of the world.

In order to make the GVDoxil regimen cheaper and less toxic, we substituted liposomal doxorubicin with high-dose dexamethasone to get a regimen called GVDex at our centre. We hypothesized that the inexpensive and non-myelosuppressive agent dexamethasone would complement the anti-lymphoma activity of chemotherapy as it is a well-known part of other salvage regimens like DHAP. Initially, we started using this regimen as a *second-line salvage regimen* (in patients who did not respond or could not tolerate DHAP/ICE). Subsequently, we extended its use as a *first-line salvage* option in both adult and paediatric patients with R/R HL.

2. Methods

At our centre, we started using the GVDex regimen as a *second-line salvage* in 2012. After noting good responses, we started using this regimen as a *first-line salvage therapy* from 2015. The chemotherapy protocol was approved by the Institutional scientific advisory committee. This study is a retrospective analysis of patients who received GVDex as a first or second salvage regimen for R/R HL. This analysis was based on data obtained from patients treated with this regimen between 2012 and 2017. Patients with relapsed/refractory Hodgkin's Lymphoma with an Eastern Cooperative Oncology Group (ECOG) performance status of 0–3 who were considered eligible for salvage chemotherapy, and subsequent consolidation with HDT and ASCT received the GVDex regimen. Forty (83%) patients had received ABVD as first-line therapy prior to relapse. Forty-six (96%) patients underwent a repeat biopsy to confirm the diagnosis prior to salvage therapy.

Patients were staged for the extent of the disease using either whole body PET-CT or contrast- enhanced computed tomography (CECT) scan of the neck, chest, abdomen, and pelvis. Baseline blood investigations included hemogram, liver function, renal function, serum lactate dehydrogenase (LDH), and serum albumin levels. Bone marrow aspiration and biopsy were done at relapse in all patients.

2.1. The GVDex regimen

GVDex was administered in an outpatient setting once in 3 weeks and consisted of gemcitabine 1000 mg/m^{2}intravenously (IV) over 30 min on days 1 and 8, vinorelbine 25 mg/m^2 intravenously (IV) bolus on days 1 and 8, and dexamethasone 40 mg orally (40 mg/m^2 in paediatric patients) on days 1–4. Palonosetron or ondansetron was used as anti-emetic prophylaxis on days 1 and 8. Complete blood counts were performed on days 1 and 8, and renal and liver function tests on day 1 of each cycle.

Treatment cycles were delayed till absolute neutrophil count (ANC) was ≥1000 cells/mm^3 or platelet counts ≥100,000 cells/mm^3 prior to day 1 chemotherapy. The day 8 dose was delivered if the ANC was ≥500/mm^3 and/or the platelet count ≥50,000 cells/mm^3. If they were lower, blood counts were repeated after 2 days and the day 8 dose was administered with a 25% dose reduction once ANC was ≥500 cells/mm^{3}and the platelet count was ≥50,000 cells/mm^3. If there were ≥4 days of delay, the day 8 chemotherapy was omitted for that cycle and the day 1 dose was reduced by 25% in the subsequent cycle. Doses of gemcitabine and vinorelbine were reduced by 25% if any grade 3 non-haematological toxicities (excepting nausea, vomiting and alopecia) were observed. In the event of grade 4 non-haematological toxicity, further chemotherapy with GVDex was withheld.

2.2. Response evaluation

Patients were evaluated after 2–3 cycles of GVDex with physical examination and PET-CT scans. Patients with PR/CR were considered for HDT/ASCT (BEAM or LACE conditioning) [16–20]. If HDT was not feasible but the patient had responded to GVDex, additional cycles were administered (maximum 6).

2.3. Analysis

CR was considered in patients with a Deauville score (DS) of 1–3 [21]. Patients with a 50% reduction in tumor size with reduced SUV_{max} but with DS 4–5 were considered as having PR [21]. Any new sites of disease or significant increase in PET uptake were considered as progression. Survival from the start of the salvage therapy was computed using the Kaplan-Meier method [22]. Progression-free survival (PFS) was measured from the first day of GVDex to first occurrence of progression or relapse, or death from any cause, or to the date of the last follow-up of surviving patients. Overall survival (OS) was measured from the date of start of GVDex to the date of death or last follow-up of surviving patients. Toxicities were captured as per CTCAE version 4.0 [23]. Data was captured until December 2018 for all patients.

3. Results

3.1. Patients

Between 2012–2017, 48 adult and paediatric patients received GVDex [median age 24 years (5–63); 32 (67%) males] (Table 1). This included 13 (27%) paediatric patients under 18 years. Almost all patients (46 patients, 96%) underwent a biopsy to prove relapsed/refractory Hodgkin's lymphoma. Of these 48, 28 (58%) received GVDex as *first salvage,* and 20 (42%) received it as their *second salvage or beyond* (16 prior DHAP, 3 prior ICE, 1 prior subtotal nodal irradiation). The median time from diagnosis to relapse was 18.9 months (2–119 months) and 20 (42%) patients had primary progressive disease (no CR or progression within 3 months of first-line therapy). Front- line therapy was ABVD in 34 patients (71%), PET-adapted ABVD followed by escalated BEACOPP in 6 (13%) [24], hybrid therapy in 5 (10%) and other

Table 1
Baseline characteristics (N = 48).

Variable	N = 48 (%)
Age, Median In Years (Range)	24 (5–63)
Sex	
Male	32 (67%)
Female	16 (33%)
Stage At Diagnosis	
Early (Stage I/IIa)	11 (23%)
Advanced (Stages IIb-IV)	37 (77%)
Bulky Disease At Diagnosis	17 (35%)
Stage At Relapse (Before Starting Gvdex)	
Early	14 (29%)
Advanced	34 (71%)
Response To First-Line Chemotherapy	
Complete Response	21 (44%)
Partial Response	4 (8%)
Refractory/Progressive Disease	23 (48%)
Time From Diagnosis To Start Of Gvdex	
< 12 Months	7 (15%)
≥12 Months	41 (85%)

chemotherapy regiments in 3 (6%) patients. Thirty-three (69%) patients had stage III/IV disease at the time of relapse. At the time of GVDex administration, performance status was 1 in 44 patients (92%), 2 in 3 patients (6%) and 3 in 1 (2%) patient.

3.2. Use of GVDex as a second salvage regimen

Twenty patients (Prior DHAP: N = 16, prior ICE: N = 3 and prior subtotal nodal irradiation: N = 1) received GVDex as second salvage for the following reasons: no response or progressive disease (N = 17), achieved partial response but GVDex given to attempt complete metabolic response (N = 2) prior to transplant, intolerance to DHAP (only 1 cycle of DHAP was delivered and response not assessed). Among the 3 patients who received ICE, all of them had switched to GVDex due to non-response.

3.3. Responses to therapy

A median of 3 (Range:1–6) cycles of GVDex was administered per patient. Two patients received 1 cycle, 11 patients received 2 cycles, 16 received 3 cycles, 17 received 4 cycles and 2 patients received 6 cycles of GVDex. Out of the 48 patients, 47 were evaluable for response. One patient received 3 cycles of GVDex and died of sepsis prior to re-assessment. All the 47 patients were included for response assessment. Among the 47 patients, 24 (51%) achieved CR and 6 (13%) achieved a PR for an overall response rate (ORR) of 64%. Among those who received GVDex as *first* salvage, the ORR was 71% (N = 20/28) with complete and partial responses in 17 (61%) and 3 (10%) patients, respectively. Among those who received GVDex as a second or further line of salvage therapy, the ORR was 50% (N = 10/20) with complete and partial responses in 7 (35%) and 3 (15%) respectively.

Among 12 paediatric (< 18 years at the time of relapse) patients, 7 received GVDex as first salvage and 5 received GVDex as second salvage after ICE/DHAP failure. The overall response rate was 58% (7/12) with complete and partial responses in 6 (50%) and 1 (8%), respectively.

3.4. Autologous stem cell collection and high-dose chemotherapy

Of the 30 patients who achieved a PR or better with GVDex salvage, stem cell collection was attempted in 22 patients. The other 8 patients did not undergo stem cell collection for the reasons as mentioned in Fig. 1. Collection was successful (≥2 million cells/kg) in 19 patients (86%). Among the patients with successful stem cell yield, the median stem cell count was 4.55 × 10^6 $CD34^+$ cells/kg (2.3–14.8). Seven patients (29%) received 1 dose of plerixafor 0.24 mg/kg SC in addition to GCSF for stem cell collection. Nineteen (45%) patients underwent ASCT. The stem cell transplant outcomes are outlined in Fig. 1.

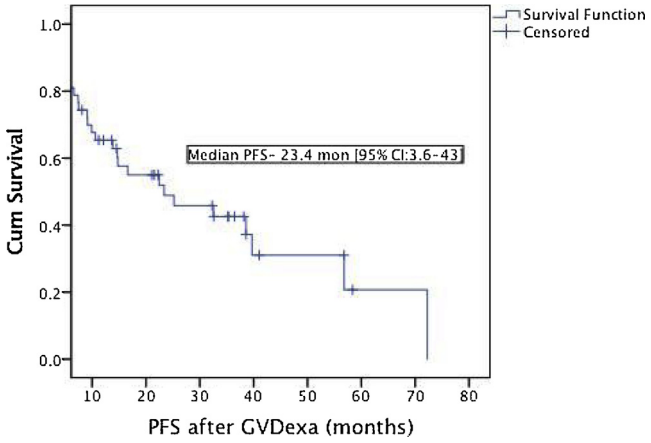

Fig. 2. Progression-free survival after the start of GVDex.

3.5. Failure of GVDex as salvage therapy

Of the 17 patients who failed to achieve CR or PR with GVDex, subsequent salvage therapy lead to PR or better in 6 patients (35%). The rest progressed after the next salvage therapy (Fig. 1).

3.6. Survival analysis

The median follow-up from the start of GVDex in this patient cohort was 20.2 months (3–61). Twenty-six (54%) patients are still alive after all treatment and 22 (46%) patients have died. All 48 patients were included in the survival analysis (intention-to-treat analysis). The median PFS was 23.4 months (95% CI:3.6–43). The median OS was 36.4 months (95% CI:29–43.6). The Kaplan-Meier survival curves are depicted in Figs. 2 and 3. The Kaplan-Meier estimate of patients alive and progression-free at 24 months was 60% and 49%, respectively. Among the 22 patients who have undergone HDT with ASCT, 9 (41%) patients have progressed and 13 (59%) patients are alive and disease-free. Of the 3 patients who underwent allogenic HSCT, 1 is alive and in remission, 1 died of chronic graft-versus-host disease and 1 patient died

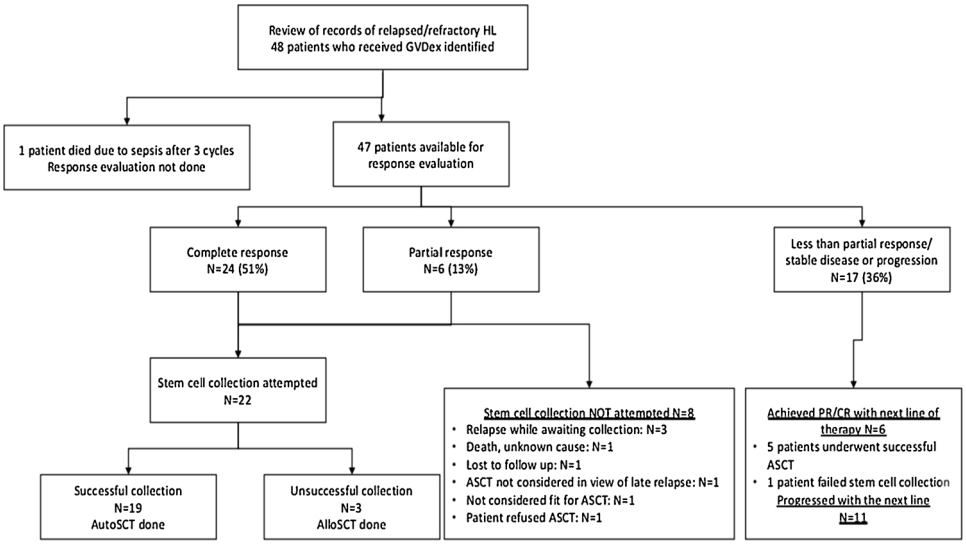

Fig. 1. Study schema.

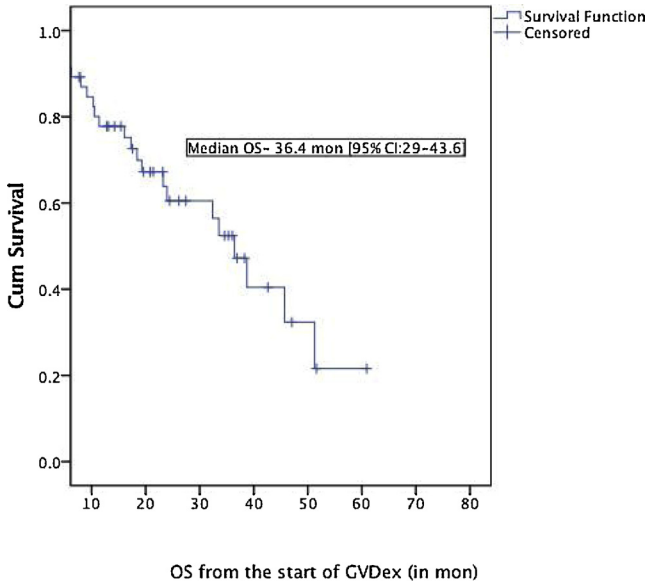

Fig. 3. Overall survival after the start of GVDex.

due to disease progression.

3.7. Toxicities of GVDex (Table 2)

Fifteen (31%) patients did not have any toxicity with GVDex. Five patients (10%) had vinorelbine-induced extravasation/venotoxicity but none required surgical intervention. One patient (2%) had treatment-related mortality: grade 5 neutropenia and respiratory sepsis. The patient was 64 years old with comorbidities of bronchial asthma, chronic kidney disease and diabetes and, developed pneumonia and neutropenic sepsis after his 3rd cycle of GVDex.

4. Discussion

The evolution of the treatment of Hodgkin's lymphoma has improved the survival of patients to more than 90% at 5 years [25]. The advent of PET scan and BEACOPP has improved the outcomes even in advanced disease and has reduced recurrences. Despite this, a small proportion of patients are either refractory or sustain an early recurrence of the disease. It is evident that a significant proportion of these patients can be treated with high-dose chemotherapy followed by autologous stem cell rescue achieving sustained durable remissions. In this context, various regimens have been administered to achieve the maximal reduction of disease prior to high-dose chemotherapy.

However, newer regimens are required that can be administered with less toxicity but comparable response rates to more conventional treatments. The availability of brentuximab vedotin and nivolumab have improved options for patients with recurrent disease. However this comes with substantial cost which is difficult to bear for the majority of patients in developing countries such as India [15]. Therefore, there is relevance in improving the conventional chemotherapy salvage regimens to enhance response, reduce toxicity and cost. It is in the latter context that gemcitabine-based regimens have gained popularity in the last 2 decades. In this analysis, we have shown that a combination of gemcitabine, vinorelbine and high-dose dexamethasone can be an *outpatient low-toxicity salvage* regimen with excellent response rates (70% when used as first line and 50% when used after 2 lines of prior therapy) in patients with relapsed/refractory HL. The regimen was stem cell friendly with most eligible patients proceeding to stem cell transplantation without collection difficulties.

The response rates of the GVDex regimen are comparable to other chemotherapy regimens used in relapsed HL (Table 3). In a direct comparison with the GV + doxil (liposomal doxorubicin), on which this regimen was modeled, we noted equivalent response rates and lesser toxicity (neutropenia rates 63% vs. 17%) [8]. High dose dexamethasone is non-myelotoxic, non-cardiotoxic and non-cross resistant with both gemcitabine and vinorelbine and, much cheaper than liposomal doxorubicin. In comparison to other popular gemcitabine-based regimens like GDP, GVDex is easier to administer and may be suitable even in a patient with renal dysfunction [11]. Though other regimens such as IGEV, IEV have produced higher response rates, these regimens were associated with higher rates of grade 3 or 4 haematological toxicity and hospital admissions when compared to GVDex [10].

The limitations of the study include the retrospective nature of the study from a single centre and represent a diverse population of patients receiving GVDex either as a first- or second- line salvage regimen after recurrence. A prospective clinical trial is needed to confirm these findings and is currently ongoing at our centre. Comparisons across studies are not robust as the populations may be different. Unfortunately, randomized trials comparing salvage regimens are unavailable due to the rarity of R/R HL. Twelve paediatric patients received this regimen at our centre (nearly one-fourth (25%) patients in this study were < 18 years of age) and demonstrated good outcomes. GVDex is a suitable regimen for young patients with R/R HL with limited long-term toxicities by avoiding the use of agents like cisplatin, alkylating drugs like ifosfamide and agents like anthracyclines which are usual components of other popular salvage regimens.

Table 2
Toxicities with GVDex regimen.

Toxicity grade	Grade 1 N (%)	Grade 2 N (%)	Grade 3 N (%)	Grade 4 N (%)
Haematological				
Neutrophils	4 (8%)	4 (8%)	5 (10%)	8(17%)
Haemoglobin	–	2 (4%)	2 (4%)	–
Platelet count	1 (2%)	–	1 (2%)	1 (2%)
Febrile neutropenia	–	–	6 (13%)	4 (8%)
Non-haematological				
CINV[a]	1 (2%)	1 (2%)	1 (2%)	–
Ileus	1 (2%)	1 (2%)	1 (2%)	–
Transaminitis	3 (6%)	–	3 (6%)	–
Gastritis	2 (4%)	2 (4%)	–	–
Constipation	1 (2%)	1 (2%)	–	–
Hypersensitivity reaction[b]	1 (2%)	–	–	–
Extravasation[b]	1 (2%)	3 (6%)	–	–
Hyperglycemia	–	2 (4%)	–	–

a. CINV- chemotherapy-induced nausea and vomiting; b. During infusion of vinorelbine.

5. Conclusions

The response rates with GVDex were comparable to those reported with GVDoxil when used as a *first-line* salvage regimen in relapsed/refractory HL. It was an effective regimen even in patients who failed 2 lines of therapy for HL. GVDex could be considered as a low-cost, effective and less toxic, non-platinum containing salvage regimen for relapsed HL.

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Table 3
Comparison of commonly used gemcitabine-based salvage regimens in relapsed Hodgkin's lymphoma.

Chemotherapy regimen	N	CR (%)	PR (%)	ORR (%)	Neutropenia ≥grade3 (%)	Thrombocytopenia ≥Grade 3 (%)
GDP (11)	23	17	52	69	9	13
GVDoxil (8)	91	19	51	70	63	14
IGEV (10)	91	53	27	80	28	20
GVDex(first line salvage)[a]	28	61	10	71	16	2
GVDex (Second line salvage)[a]	20	36	11	50	10	2

CR: complete response, PR: partial response; ORR: overall response rate.
G: gemcitabine, V; Vinorelbine; Doxil: liposomal doxorubicin; P: cisplatin; D: high dose dexamethasone: I: ifosfamide; E: etoposide.
a. Current study.

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