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Outcomes of Gemcitabine, Vinorelbine, and Doxorubicin in Peripheral T-Cell Lymphoma

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Abstract

Peripheral T-Cell Lymphoma (PTCL) remains a difficult-to-treat heterogeneous group of Non-Hodgkin Lymphomas. Our current treatment guidelines have been largely based on studies evaluating the treatment of B-cell Lymphomas, in which there were small subsets of T-cell lymphoma patients included. Additionally, there is no clear guideline for sequencing of subsequent salvage regimens. Prior retrospective studies have reported activity with the combination chemotherapy, Gemcitabine, Vinorelbine, and Doxorubicin (GVD) in the treatment of relapsed and refractory PTCL, but these have been international retrospective analyses. Thus, we performed a retrospective analysis within our own institution of the efficacy and safety of GVD in the treatment of relapsed and refractory PTCL. We found an overall response rate of 80%, complete response rate of 50%. Complete response rates were higher in patients receiving GVD as second-line therapy as compared to later lines of therapy. GVD was well tolerated with the most common adverse effects being neutropenia, infection, and peripheral neuropathy. Ultimately, our data supports the use of GVD in relapsed and refractory PTCL, with possible greatest benefit when used as second-line therapy.

Keywords: T-cell Lymphoma; Peripheral T-cell Lymphoma; Non-Hodgkin Lymphoma; Gemcitabine; Vinorelbine; Doxorubicin

Introduction

Peripheral T-Cell Lymphoma (PTCL) is a heterogeneous group of lymphoid neoplasms that account for approximately 10% of all Non-Hodgkin Lymphomas (NHL) [1]. PTCL subtypes are defined by distinct histologic and pathologic features with the three most common being PTCL-not otherwise specified (NOS), angioimmunoblastic T-cell lymphoma (AITL), and Anaplastic Large Cell Lymphoma (ALCL) with or without ALK mutation [2,3]. Furthermore, PTCL-NOS is a broad category of biologically and clinically variable lymphomas not meeting criteria for other established PTCL diagnostic entities [4]. Despite this heterogeneity, standard of care (SOC) frontline therapy remains an anthracycline-based chemotherapy regimen [5]. Cyclophosphamide, Doxorubicin, Vincristine, Prednisone with Etoposide (CHOEP) has shown 3-year Overall Survival (OS) rates ranging from 54-67% for AITL, ALCL (ALK-negative), and PTCL-NOS [6]. More recently, Brentuximab vedotin with Cyclophosphamide, Doxorubicin, Prednisone (A-CHP) showed a 5-year OS of 70% for CD30-positive PTCL patients [7]. Additionally, patients should be considered for consolidative autologous stem cell transplant (autoSCT), though data on outcomes remain mixed [8-10].

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Despite these first-line therapies, between 68-75% of patients will have relapsed or refractory (R/R) disease, with median OS of about 5.8 months [11,12]. Currently, there is no clear guideline for sequencing recommended second-line and salvage regimens. Gemcitabine, Vinorelbine, and Doxorubicin (GVD) was originally evaluated in the CALGB 59804 trial in the treatment of r/r Hodgkin Lymphoma (HL) showing significant activity with an Overall Response Rate (ORR) of 70% [13]. Subsequent studies have demonstrated the effectiveness of GVD for r/r aggressive Non-Hodgkin Lymphoma (NHL) with an ORR of 36% and Compete Response (CR) rate of 25%. This included a smaller number of patients with either PTCL or ALCL [14]. Most relevant is a retrospective study from Tianjin Medical University that evaluated GVD in the treatment of r/r TCL, in which they report an ORR of 65.2%, CR rate of 29%, 36 month median OS, and 5-year OS of 32.4%.14 These response rates were similar to other salvage regimens such as Ifosfamide, Carboplatin, Etoposide (ICE) and Dexamethasone, High-dose Ara-C, and Cisplatin (DHAP), but had fewer myelosuppressive side effects [15,16]. While this study suggests activity of GVD in r/r PTCL, the reported clinical characteristics, including demographics and histologic subtypes were limited and not reflective of the diverse patient population within our own clinical practice. To date, there has not been a similar retrospective analysis performed within the United States. Thus, our retrospective study aims to evaluate outcomes and toxicities specifically within PTCL patients treated with GVD within our institution.

Patients and Methods

Patients:

Patients were identified for this retrospective study who received GVD as a subsequent line of therapy for r/r PTCL between January 2015 and December 2020 at the University of California, Davis Cancer Center. Patients eligible for analysis met the following criteria: received a histopathologic diagnosis of a subtype of PTCL including: PTCL-NOS, ALCL, AITL, Mycosis Fungoides (MF), Sezary Syndrome (SS), or Adult T-Cell Leukemia/Lymphoma (ATLL), age > 18, had relapsed or refractory disease after SOC first-line therapy. Patients were excluded if they had a histopathologic diagnosis of Primary Cutaneous ALCL, Subcutaneous panniculitis-like TCL, T-cell Large Granular Lymphocytic Leukemia (T-LGL), T-cell Prolymphocytic Leukemia (TPLL), or TCL of unknown subtype. We collected the following clinical characteristics of the enrolled patients retrospectively: patient demographics, histopathologic subtype, Ann Arbor stage, Eastern Cooperative Oncology Group (ECOG) performance status, International Prognostic Index, total prior lines of therapy, time to relapse, autoSCT status, response imaging (Lugano criteria), duration of follow-up, date of death, and cause of death.

Treatment

The treatment protocol consisted of patients receiving Gemcitabine 800-1000 mg/m2, Vinorelbine 15-20 mg/m2, and Doxorubicin 10-15 mg/m2, given on days 1 and 8 of 21-day cycles for up to 6 cycles. Patients were given prophylactic oral Ondansetron 16mg and oral Dexamethasone 8mg at least 30 minutes prior to administration of chemotherapy with each cycle. All patients underwent routine examination and standard lab testing including complete blood count, renal, and liver function testing prior to each cycle. If labs were within treatment parameters prior to each cycle, then chemotherapy was administered. Treatment parameters included: Absolute Neutrophil Count (ANC) > 1,000, Platelets (PLTs) > 75,000, Serum Creatinine (SCr) < 2.0 mg/dL, and Total Bilirubin (T bili) < 2.0 md/dL. If labs did not meet parameters, then treatment was delayed by 3-7 days until recovered prior to each subsequent cycle.

Response Evaluation

All patients were assessed with routine complete history and physical exam, laboratory tests, and imaging either as CT or PET/CT obtained after at least 2 cycles. Response was classified based on imaging as either Complete Response (CR), Partial Response (PR), Stable Disease (SD), and Progressive Disease (PD) based on the Lugano response criteria.17 Overall Response Rate includes patients who achieved CR and PR. Adverse effects (AEs) were also observed and graded based on National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 5. Overall survival (OS) was calculated from the date of start of treatment with GVD (Cycle 1, Day 1) to the date of death due to any cause or date of last follow-up. Progression free survival (PFS) was measured from the time of start of treatment to the date at which there was disease relapse or death due to any cause. Time to best response was measured from date of treatment start to time of CR or stable disease.

Statistical Method

Patient and lymphoma characteristics were summarized using descriptive statistics and compared between histologic subtypes using chi-squared test or Fisher's exact test for categorical variables and the Student's t-test or Mann-Whitney U test for continuous variables. The probability of OS and PFS was calculated from the time of diagnosis to the date of progression or to the date of death from PTCL for analyses of PTCL-related mortality. Kaplan-Meier methodology and log rank test were used to examine ORR, OS, PFS. Patients alive at study end date were censored at this date or last known follow up. Univariate and multiple Cox proportional hazard models were used to obtain hazard ratio estimates and 95% confidence intervals for clinical variables of interest. For all statistical investigations, tests for significance will be two-tailed. A p-value of less than the 0.05 significance level was considered statistically significant.

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Results

Patient Characteristics:

In reviewing our electronic medical records database, we identified a total of 15 patients who had received GVD within our institution during the dates specified above. Ten of these 15 patients received GVD for a diagnosis of a subtype of R/R PTCL. Table 1 shows the demographics of these patients. Nine patients were male and one female with a median age of 55.0 years (44.5-79.2). Of the 10 total patients, 5 (50%) had a diagnosis of PTCL-NOS while 2 (20%) had AITL, 2 (20%) had MF, and 1 (10%) had ATLL. Four patients had early-stage disease (1 with PTCL-NOS, 1 with AITL, and 2 with MF). The remainder of patients (60%) have advanced disease (stage III-IV). Early relapse or refractory disease was defined as relapse or persistent disease within 12 months of starting first-line therapy. Seven patients (70%) were deemed to have early relapse or refractory disease. The remaining 3 patients (30%) had late relapse (>12 months after start of first-line therapy). For first-line treatments, 5 patients received CHOEP, 1 patient received dose-adjusted EPOCH, 1 received A-CHP, 1 patient received methotrexate. The two MF patients received skin-directed therapy as first line. Two patients went on to receive consolidative autoSCT after first-line therapy. Both had a diagnosis of AITL and achieved CR after 6 cycles of CHOEP prior to undergoing transplant.

Five (50%) patients received GVD as second-line therapy and received a median of 4 cycles. Four patients received GVD as third-line therapy, with a median of 3 cycles. One patient received GVD as fifth-line therapy and received 2 cycles. One patient underwent haploidentical allogeneic SCT after second-line GVD. One patient underwent autoSCT after third-line GVD.

Table 1: Patient characteristics.

	Total population N = 10 (% or range)
Median age at diagnosis	55.0 (44.5-79.2)
Sex	
Male	9 (90.0)
Female	1 (10.0)
Race	
Caucasian	6 (60.0)
African American	2 (20.0)
American Indian	1 (10.0)
Unspecified	1 (10.0
PTCL Subtype	
PTCL, NOS	5 (50.0)
AITL	2 (20.0)
Mycosis fungoides	2 (20.0)
ATLL	1 (10.0)
Stage at diagnosis	
III - IV	6 (60.0)
I - II	4 (40.0)
Stem cell transplant	4 (40.0)
Relapse	
Early (≤12 months)	7 (70.0)
Late (>12 months)	3 (30.0)
First-Line Therapies	
CHOEP	5 (50.0)
DA-EPOCH	1 (10.0)
A-CHP	1 (10.0)
Methotrexate	1 (10.0)
Skin-directed therapy (for MF)	2 (20.0)
GVD Line of Therapy	
Second-line	5 (50.0)
Third-line	4 (40.0)
≥Fourth-line	1 (10.0)

Abbreviations: AITL, angioimmunoblastic T-cell lymphoma; ATLL, adult T-cell lymphoma; NOS, not otherwise specified; PTCL, peripheral T-cell lymphoma; CHOEP, Cyclophosphamide, Doxorubicin, Vincristine, Prednisone with Etoposide; DA-EPOCH, Dose-Adjusted Etoposide, Prednisone, Vincristine, Cyclophosphamide, doxorubicin; A-CHP, Brentuximab vedotin with Cyclophosphamide, Doxorubicin, Prednisone; MF, Mycosis Fungoides.

Response:

All 10 patients were included in the response analysis (Table 2). The ORR rate was 80% (8 patients) with a CR rate of 50% (5 patients) and PR rate of 30% (3 patients). Median time to best response was 1.8 months (0.5-5.5 months). Of the 5 patients who received GVD as second-line therapy, 4 patients achieved CR. One patient had stable disease after second-line GVD. Of the 4 patients who received GVD as third-line therapy, 1 patient achieved CR while 3 patients achieved PR. The one patient who received GVD as fifth-line therapy had stable disease (Table 3).

Table 2: Responses and outcomes.

	Total population N = 10 (%, range or 95% CI)
Overall response	8 (80.0)
Complete response	5 (50.0)
Partial response	3 (30.0)
Median time to best response (months)	1.8 (0.5-5.5)
Median prior lines of therapy	1.5 (1-4)
Median duration of response (months)	2.5 (0.4-48)
Median follow-up time (months)	30.0 (4.8-100.5)
Overall survival (months)	5.6 (3.8-NR)
Progression-free survival (months)	4.6 (3.3-NR)

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Table 3: Patients Outcomes

GVD line of therapy	Response Rate
Second-line (N=5)	CR = 4 (80%)
	PR = 0 (0%)
	SD = 1 (20%)
Third-line (N=4)	CR = 1 (25%)
	PR = 3 (75%)
	SD = 0
≥Fourth-line (N=1)	SD = 1 (100%)

Survival:

As shown in Figure 1, at a median follow-up of 30 months (4.8 - 100.5 months), the median OS was 5.6 months (95% CI: 3.8 - not reached [NR]). Median PFS was 4.6 months (95% CI: 3.30 - NR).

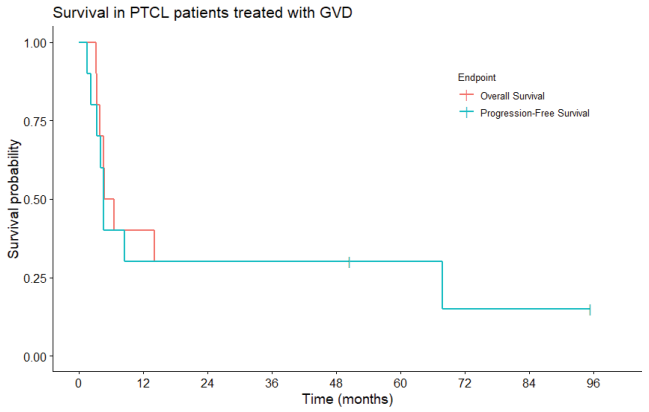

Figure 1: Kaplan-Meier estimates of overall survival and progression-free survival in patients who were given GVD.

Table 4: Adverse events.

Adverse Event	Any Grade	Grade 3 or 4
	Number of patients (%)	
Neutropenia	6 (60.0)	3 (30.0)
Infection	4 (40.0)	3 (30.0)
Peripheral neuropathy	3 (30.0)	1 (10.0)

Treatment Tolerability:

The most frequent observed AEs were neutropenia (60%), infection (40%), and peripheral neuropathy (30%) as shown in Table 4. The most common grade 3-4 AEs were febrile neutropenia (30%) and respiratory infection (30%). Two patients (20%) required at least one dose reduction due to AEs. At the time of this review, 8 of 10 patients had died. Three patients died due to complications of progressive disease. Other causes of death included respiratory failure, pulmonary hemorrhage, and sepsis. No deaths were thought to be treatment related.

Discussion

PTCL remains a difficult to treat heterogeneous group of NHLs. Current guidelines for the treatment of T-cell NHLs are primarily based on our knowledge and treatments for B-cell NHLs. Thus, response rates for T-cell NHLs to these regimens have been historically lower. Although first-line therapies remain modestly effective, still upwards of 75% of patients will have relapsed or refractory disease. Furthermore, there is a paucity of data to support the sequencing of subsequent lines of therapy.

In evaluating the efficacy of GVD in r/r PTCL, Qian et al, reported in their retrospective analysis an ORR of 65.2%, a mOS of 36 months, and a 5-year OS of 32.4%. These response and survival rates are similar to other salvage regimens such as ICE and DHAP. This study was performed at a single, international institution. To our knowledge, there is limited to no available data assessing the safety and efficacy of GVD specifically in the treatment of r/r PTCL in the US. Thus, we report our findings of the efficacy of GVD in treating r/r PTCL at our single institution.

Our results showed that GVD produced robust response rates with an ORR of 80% and CR of 50%. A greater number of patients achieved CR when they received GVD as second-line therapy, possibly suggesting better efficacy when used as an earlier line of salvage therapy. While our estimated OS and PFS were lower than previously reported, we recognize this is based on our smaller sample size of patients. We also included patients who had received up to four prior lines of therapy and thus could have had more advanced and/or refractory disease at the time of GVD initiation. This is further supported by the fact that at the time of review, 8 of the 10 patients had died.

GVD was well tolerated among the 10 patients included in our evaluation with the most common AEs being neutropenia, infection, and peripheral neuropathy. Grade 3-4 AEs occurred in 30% of patients and only 20% of patients required dose reductions. Additionally, no deaths were deemed due to treatment. Despite the limitations of our small sample size, our retrospective review supports the effectiveness of GVD in treating r/r PTCL and possibly best utilized early in subsequent lines of therapy for r/r PTCL. Further prospective and randomized controls trials with larger sample sizes are needed to fully assess the efficacy, safety, and survival benefits of GVD in treating r/r PTCL.

Conclusion

Our single-institution retrospective analysis shows a robust response rate, tolerable safety profile, and potential survival benefit for the use of GVD in the treatment of r/r PTCL with potential greatest benefit in the second-line setting.

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