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Gemcitabine-vinorelbine-prednisolone combination in cases with lymphoma: retrospective analysis

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Abstract

Objective: The aim of this study is to evaluate the response rate with gemcitabine-vinorelbine-prednisoloe (GVP) combination in cases with relapsed/refractory lymphoma.

Method: Forty-four patients with lymphoma, 22 with Hodgkin lymphoma (HL) and 22 with non-Hodgkin lymphoma (NHL), treated by GVP combination regimen were evaluated retrospectively.

Results: Complete response (CR) and partial responses (PR) were detected in 6 and 8 cases, respectively and overall response rate was 63.63% in cases with HL. Although autologous stem cell transplantation could be done in only 2 cases, long term survival was achieved in cases responsive to GVP regimen. Among NHL cases only 1 CR and 3 PRs were detected in cases with diffuse large B cell lymphoma with 5-7 months response duration. One minimal response and 1 PR were detected in 2 cases with peripheral T cell lymphoma with 2-4 months of response duration. There was no response in grey zone lymphomas.

Conclusion: GVP regimen is highly active in cases with HL both in primary refractory and also relapsed/refractory (R/R) HL cases and may be performed in outpatient clinic.

Introduction

High dose chemotherapy (HDCT) and autologous stem cell transplantation (ASCT) is standard of care in relapsed and/or refractory cases with HL and NHL. However, there is no optimal salvage regimen in these cases. Both HL and NHL are curable disease among malignant diseases, but 20-40% of the cases relapse. Salvage treatment with non-cross resistant drugs is standard approach in fit patients. Response to salvage regimen is very important for ASCT and long-term survival. However, there is no ideal salvage regimen and it is critical to obtain maximum response [1-3]. Of course, all patients are not fit enough for ASCT due to co-morbidities and/or patients' preferences. For this reason, ideal regimen must have a potential for higher response rate with long remission duration and acceptable toxicity profile. There are many combination treatments for this aim [4-6]. DHAP and ICE are the most commonly used salvage regimens and CORAL study is the only Phase III randomized study at this field [8]. The two important points are the heterogeneity of lymphomas and also doctors treating these patients.

Gemcitabine containing regimens are important choices in daily practice and response rates with these combinations may be as high as 70-85% [9]. These are effective regimens with acceptable toxicity profile allowing stem cell collection and also to use in outpatient clinics.

Here we presented 44 cases with lymphoma treated by GVP regimen and discussed available literature.

Patients and methods

Forty-four cases with lymphoma treated by GVP regimen were evaluated retrospectively. Twenty-two of the cases had HL and 22 had NHL. GVP regimen was performed in every 3 weeks with G-CSF support. Gemcitabine was given 800mg/m2 in days 1 and 8, vinorelbine was given 25 mg/m^2 in days 1 and 8 and prednisiolone was given 100 mg per day between 1 and 8th days. Rituximab was added in cases with CD20 expression.

Patients were treated in outpatient clinic. Response was assessed with standard criteria after 3 cycles of treatment by using PET/CT and /or CT scanning's. ASCT was performed in cases with at least PR after 3cycles. GVP regimen was given for six cycles in patients rejecting ASCT and showing at least PR.

Findings

Forty-four patients with lymphoma were included in this retrospective analysis. Age range was between 18 and 77; 19 of them were female and 25 were male. Twenty-two of the cases had HL and 22 had NHL.

HL cases

Age range was between 21-59; mean age was 40.4 ± 14.3, female/male ratio was 10/12. All the patients had been treated by ABVD regimen as first line therapy. Three of the cases had primary refractory

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disease, 5 cases had relapse disease before 12 months and 14 cases had relapse after 12 months from the end of first line treatment.

GVP regimen was given as first line salvage therapy in 3 cases. CR was detected in 2 of these 3 cases: one did not accept ASCT, and is in CR more than 25 months after GVP. Nivolumab was given to the second patient after progression of the disease and she is still receiving immunotherapy, response duration to GVP was 4 months in this case. Progressive disease (PD) developed in third case, and he died in spite of bendamustine and brentuximab vedotin (BV) treatments.

GVP regimen was given as second line salvage treatment to 19 cases; 3 of them had primary refractory disease, PD was detected in 2 cases and they died with disease progression. One of these 3 cases achieved CR and ASCT was performed and she is alive (118+ months). Sixteen patients had relapse disease after than 12 months; DHAP, ICE and local radiation had been given to 13, 2 and 1 cases, respectively. Among these cases CR was detected in 3 cases; ASCT was rejected by the patients and they are alive (6-90+ months). PR was detected in 6 cases; ASCT was performed in one case and she is alive, five cases rejected ASCT; PD occurred in 4 cases: 3 died one lost to follow up. Five cases relapsing less than 12 months and receiving GVP as second line salvage, PR was detected in 2 cases and remission duration was 6 months in one. Other case was in remission for 25 months with GVP regimen. BV and bendamustine were given after progression and lastly, she is receiving nivolumab. CR was achieved in one case, remission duration was 35 months, IGEV and then BV were given for relapses, but she died with progression. PD developed in 2 cases; one lost to follow up and second died in spite of bendamustine, BV, lenalidomide. Table 1 shows the demographic and treatment details of the patients with HL.

NHL cases

Among these cases, twelve had diffuse large B cell lymphoma (DLBCL), 6 had peripheral T cell lymphoma (PTCL), 3 had grey zone lymphoma between DLBCL and HL and one had anaplastic lerge cell lymphoma (ALCL).

DLBCL cases

Male/female ratio was 6/6, age range was 30-77, mean 48.9 ± 13.3, R-GVP was given as second line salvage in all but one case. Relapse had been detected in seven cases less than 12 months from the end of first line R-CHOP therapy; CR, PR and PD were detected in 1, 2 and 4 cases, respectively. ASCT was rejected by the patients and response durations were 5, 6 and 7 months in CR and PR patients but they died in spite of second line salvage regimens. Relapse occurred in five cases more than 12 months from the end of first line therapy. PR was detected in only one case and radiation was used for local relapse and she is alive. Cases with PD died in spite of third line salvage treatments.

PTCL cases

Three of 6 cases received GVP as first and 3 received as second line salvage regimen. Two of these cases had transformed disease from mycosis fungoides. Relapse developed less than 12 months after first line treatment in all cases, except one. Minimal response was detected in one case and he lost to follow up. PR was detected in one case, but she died after 4 months. PD was detected in 4 cases; 2 died and new treatments were planned in 2 cases.

Table 1. Demographic and treatment details of the patients with HL.F: female, M: male, NS: nodular sclerosing, MC: mixed cellular, NC: not characterized, ABVD: doxorubicin-bleocin-vinblastine-DTIC, CR: complete response, PR: partial response, PD: progressive disease, MR: minimal response, GVP: Gemcitabine-vinorelbine-prednisolone, DHAP: dexamethasone, Ara-C-cisplatinum, ICE: ifosfamide-carboplatin-etoposide, IGEV: ifosfamide-gemcitabine-vinorelbine, PEPC: procarbazine-etoposide-prednisolone-cyclophosphamide, BV: brentuximab vedotine, ASCT: autologous stem cell transplantation, A: alive, E: exitus, LFU: lost to follow up.

Patient Number	Age	Sex	Stage	Subytpe First treatment	Response to 1. treatment	Relapse Date (Month)	1.treatment at relapse/response/ response duration (month)	2.treatment at relapse/response/ response duration (month)	Treatment after GVD/Response	Survival time (month)	Last status
1	50	F	II-B	NS/ABVD	CR	>12	**GVP / CR / 4**	Nivolumab	Nivolumab	63+	A
2	58	M	II-A	MC/ABVD	CR	>12	**GVP / CR / 25+**	-	-	64+	A
3	59	M	III-B	NS/ABVD	PR	<12	**GVP / PD**	Bendamustine / PD	BV / PD	16	E
4	39	M	II-B	NS/ABVD	Refractory	-	DHAP / PD	**GVP / PD**	BV / PD	12	E
5	20	F	IV-B	NC/ABVD	CR	>12	DHAP / PD	**GVP / PR**	ASCT	102+	A
6	50	M	II-B	NC/ABVD	CR	<12	ICE / PD	**GVP / PR / 5**	BV / PD	59	E
7	57	M	III-B	MC/ABVD	CR	>12	DHAP / PR	**GVP / PD**	-	75	E
8	22	F	I-A	NS/ABVD	CR	>12	DHAP / PR	**GVP / PR / 25**	BV-Bendamustine-Nivolumab	144+	A
9	21	F	II-A	NS/ABVD	Refractory	-	DHAP / PD	**GVP / PD**	-	13	E
10	46	F	I-A	MC/ABVD	PR	<12	DHAP / PR	**GVP / CR / 35**	IGEV-BV	93	E
11	49	M	II-A	NS/ABVD	CR	>12	DHAP / CR	**GVP / PD**	-	41	E
12	37	M	II-A	NC/ABVD	CR	<12	DHAP / PD	**GVP / PD**			LFU
13	58	F	IV-B	MC/ABVD	PR	<12	DHAP / PR	**GVP / PR / 6**	PEPC	33	E
14	23	M	III-B	NS/ABVD	CR	>12	DHAP / PR	**GVP / CR / 90+**	-	133+	A
15	30	F	III-B	NS/ABVD	Refractory	-	DHAP / PD	**GVP / CR**	ASCT	118+	A
16	57	F	III-B	NS/ABVD	CR	>12	DHAP / PD	**GVP / PR / 12**	-	34	E
17	29	M	III-A	NS/ABVD	PR	>12	DHAP / PR	**GVP / PR / 6**	-	24	E
18	27	F	IV-B	NS/ABVD	CR	>12	DHAP / PD	**GVP / PD**	BV-Bendamustine -ASCT	77+	A
19	54	F	I-A	NC/ABVD	CR	>12	DHAP / CR	**GVP / PR / 6**	Bendamustine	75+	A
20	27	M	III-A	NC/ABVD	CR	>12	DHAP / CR	**GVP / CR / 30+**	-	94+	A
21	27	M	III-A	NS/ABVD	PR	<12	ICE-ASCT / PR	**GVP / PD**	BV-Bendamustine-Lenalidomide	70	E
22	49	M	IIIB	NS/ABVD	CR	>12	Radiation / CR	**GVP / CR / 6+**	-	284+	A

ALCL case

PR was detected in this case and ABVD was given as third line therapy and he is alive.

DLBCL/HL cases

R-GVP was given as second line in 2 cases and as third line salvage in one case. All of these cases PD developed, and they died. Table 2 shows the demographic and treatment details of the patients with NHL.

Discussion

Salvage chemotherapy and high dose chemotherapy supported by ASCT is the standard of care in cases with R/R lymphoma. However, there is no standard or optimum salvage regimen in these cases. DHAP and ICE are the most commonly used regimens. Gemcitabin containing regimens may be effective, cheaper and non-toxic alternatives in cases with R/R lymphoma and may be used in outpatient clinics.

Gemcitabine is a cytarabine analog and is a pyrimidine antimetabolite inhibiting DNA synthesis [10,11]. Gemcitabine containing regimens are more effective than single agent gemcitabine and most commonly used drugs in these regimens are vinorelbine, doxorubicine, ifosfamide, cisplatinum and steroids [12-15].

GDP (gemcitabine-dexamethasone-cisplatinum) is an active regimen in cases with R/R lymphoma, with response rates as high as 50% and 70% in NHL and HL, respectively. Stem cell mobilization is feasible with this regimen and GDP has been found non-inferior to DHAP regimen which is most commonly used salvage regimen as mentioned before [16-19]. In a large study containing 235 patients GDP has been used in cases with R/R lymphomas and response rate has been found to be 49% and 71% in cases with NHL and HL, respectively with acceptable toxicity profile [20]. IGEV is another option in RR cases with HL with acceptable toxicity profile and feasible for stem cell collection [21]. Doxorubicine has been used in some series in addition to gemcitabine and vinorelbine with variable doses and intervals. Response rates have been found as 65.2% in cases with R/R T cell lymphoma, 48.6% in R/R NHL and 70-80% in R/R HL [22-24]. Although these regimens have been found to be highly effective, doxorubicine using may be problem in some cases. It is very well known that ABVD and R-CHOP which are standard regimens for HL and NHL for first line therapy. For this reason, doxorubicine containing gemcitabine-vinorelbine regimens are not feasible in some cases in spite of high response rates. This is important especially in cases with limited cardiac function receiving this drug in first line setting.

Gemcitabine, vinorelbine and steroid containing regimens have been used in some series, but number of the patients is limited in these series. Rituximab has been added to gemcitabine and vinorelbine in 4 cases with TCRBCL and 3 CR and 1 PR have been reported [25]. Gemcitabine-vinorelbine-prednisolone (GVP) regimen has been used in 50 cases with R/R HL and response rate has been found as 77.5% in evaluable 4 cases [26]. In our analysis CR has been found in 2 of 3 cases with R/R HL when used as first line salvage regimen. Both of 2 cases achieving CR rejected ASCT; response duration was 4 months in one and 25 months in other case. Although the number of the patients are limited, this suggests that GVP is highly active salvage regimen in cases with R/R HL. In our cases, 19 cases receiving GVP as second line salvage regimen, CR was detected in one case with primary refractory HL which is difficult to treat. This case is alive at 118+ months and this is very important for these cases due to the difficulty of the therapy of these cases. Long term survival as long as 90 months was achieved in our cases achieving CR and PR in cases relapsing more than 12 months. These results suggest that GVP is feasible regimen in cases with late

Table 2. Demographic and treatment details of the patients with NHL. F: female, M: male, DLBCL: diffuse large B cell lymphoma, PTCL: peripheral T cell lymphoma, PTCL Tr: peripheral T cell lymphoma transformed disease, ALCL: anaplastic large cell lymphoma, CR: complete response, PR: partial response, PD: progressive disease, MR: minimal response, GVP: Gemcitabine-vinorelbine-prednisolone, R: rituximab, DHAP: dexamethasone, Ara-C-cisplatinum, ICE: ifosfamide-carboplatin-etoposide, IGEV: ifosfamide-gemcitabine-vinorelbine, IIVP: ifosfamide-idarubicine-vinblastine-prednisolone, PEPC: procarbazine-etoposide-prednisolone-cyclophosphamide, BV: brentuximab vedotine, ASCT: autologous stem cell transplantation, A: alive, E: exitus, LFU: lost to follow up.

Patient Number	Age	Sex	Stage	Subytpe/1. treatment	Response to 1. treatment	Relapse Date (Month)	1.treatment at relapse/ response/response duration (month)	2.treatment at relapse/response/ response duration (month)	Treatment after GVD/Response	Survival time (month)	Last status
1	46	F	II-A	DLBCL/RCHOP	CR	>12	R-DHAP / PD	**R-GVP / PD**	-	90	E
2	77	F	IV-B	DLBCL/R CVP	PD	<12	R-Bendamustine / MR	**R-GVP / PD**	-	16	E
3	30	F	IV-B	DLBCL/RCHOP	CR	>12	R-DHAP / PD	**R-GVP /PD**	-	12	E
4	69	F	II-A	DLBCL/RCHOP	CR	>12	R-DHAP / CR	**R-GVP / PD**	PEPC	109	E
5	51	F	III-A	DLBCL/RCHOP	PD	<12	R-DHAP / PR	**R-GVP / CR / 5**	PEPC	27	E
6	51	M	III-A	DLBCL/RCHOP	PD	<12	R-DHAP / PD	**R-GVP / PR / 6**	DICE	12	E
7	32	M	IV-B	DLBCL/RCHOP	PR	<12	R-DHAP / PD	**R-GVP / PR / 7**	BV	18	E
8	65	M	II-A	DLBCL/RCHOP	CR	<12	R-DHAP / PR	**R-GVP / PD**	-	19	E
9	50	M	III-A	DLBCL/RCHOP	CR	>12	**R-GVD / PD**	**-**	-	69	E
10	60	F	III-B	DLBCL/REPOCH	CR	>12	R-Bendamustine / PR	**R-GVP / PR**	Radiation	32+	A
11	52	M	III-B	DLBCL/RCHOP	CR	<12	R-DHAP / PD	**R-GVP / PD**	-	12	E
12	45	M	II-A	DLBCL/RCHOP	PD	<12	R-DHAP / PD	**R-GVP / PD**	-	23	E
13	43	M	III-A	PTCLTr/CHOEP	CR	<12	**GVP / PD**	BV planned		26+	A
14	58	M	III-A	PTCLTr/CHOP	PR	>12	**GVP / MR / 2**			?	LFU
15	35	F	IV-B	PTCL/CHOP	PD	<12	DHAP / PD	**GVP / PD**	-	11	E
16	18	M	I-A	PTCL/CHOP	CR	<12	DHAP / PD	**GVP / PD**	HD Mtx	22	E
17	43	M	IV-B	PTCL/CHOEP	CR	<12	**GVD / PD**	Pralatrexate planned		14+	A
18	48	F	IV-B	PTCL/CHOEP	PR	<12	**GVP / PR / 4**	-		11	E
19	58	M	III-A	ALCL/CHOP	CR	>12	**GVP / PR**	ABVD		65+	A
20	54	M	I-A	DLBCL-HL/RCHOP	PD	<12	R-ICE / PR	**R-GVP / PD**		13	E
21	46	M	III-B	DLBCL-HL/ABVD	PD	>12	DHAP / PD	GEMOX /PD	**R-GVD /PD**	125	E
22	45	F	IV-B	DLBCL-HL/RCHOP	PD	<12	R-DHAP / PD	**R-GVP / PD**	IIVP	34	E

relapse HL. PR was detected in 2 of 5 cases with early relapse HL and this is an advantage in this high risk disease situation. In conclusion GVP is an important choice in cases with HL both in primary refractory also in early/late relapses.

There is no large study about the efficacy of GVP regimen in cases with DLBCL and we could not compare our results with others. Although more than half of our cases had unfavorable outcome with early relapse, response was not good enough. We used GVP as second line salvage regimen and 2 PR and 1 PR were detected, and remission duration was 5-7 months and ASCT was rejected by our patients. Our results suggest that GVP is not a good choice in cases with DLBCL as second line salvage regimen.

Gemcitabine and vinorelbine with or without steroids have been used in cases with lymphoma especially in cutaneous/noncutaneous T cell lymphomas but in limited number of the cases. In a small series PR has been detected in 4 of 4 cases with cutaneous T cell lymphoma [27]. We treated 6 cases with PTCL, half in first line and half in second line setting. Although gemcitabine containing regimens have been found to be effective in T cell lymphomas, our results were unsuccessful. This may be due to the early relapse in 5 of 6 cases and also transformed disease status in 2 cases.

We treated 3 cases with grey zone lymphoma with GVP and none of these cases responded. It is very well known that grey zone lymphomas have poor outcome with no response to conventional treatments. We did not find a comparable series at this matter.

In conclusion GVP regimen is feasible and effective salvage regimen with high response rate in cases with R/R HL cases both in first line and second line setting. However this regimen is not found to be good enough in cases with R/R NHL

Conflicts

No conflicts of interest

Ethical approval

This study has been approved by Cukurova University Medical Faculty Ethical comitte for non-invasive research.

This is a retrospective analysis, there is no specific informed consent received from the patients for this study. However, all the patients are informed about the medical procedures and therapeutic choices at the admissions.

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