GDP versus DHAP in relapsed and refractory Hodgkin disease

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Abstract: Background: cisplatin and gemcitabine have synergistic action, high response rate (RR), manageable hematological and non-hematological toxicity in patients with solid tumors. Our study aims to assess and compare RR and toxicity of gemcitabine, dexamethasone, and cisplatin (GDP) versus dexamethasone, cytarabine, and cisplatin (DHAP) in relapsed and refractory Hodgkin disease. **Patients and methods:** Fifty eight patients with pathologically proven HL were managed with doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) as a first line of treatment, relapsed and refractory patients in (40%) of patients were randomized into two groups; ***group A***: Received GDP and ***group B***: received DHAP. **Results:** RR was 67% in group **A** and in group **B** it was 64%, thus GDP had a higher response rate than DHAP .Treatment toxicity was lower in group A (Grade 3/4 nutropenia in (8%), vomiting in (17%) and thrombocytopenia TCP in (17%) of patients respectively) compared to treatment toxicity in group B (Grade 3/4 neutropenia in (82%) of patients, vomiting in (27%) of patients and TCP in (64%) of patients). **Conclusion**: GDP is an active outpatient treatment with limited treatment toxicity in comparison to DHAP for patients relapsed or refractory Hodgkin's disease who are unfits for autologous stem cell transplantation.
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Keyword: GDP, DHAP, Hodgkin disease

Introduction:

Hodgkin lymphoma (HL) accounts for approximately 10 % of all lymphomas diagnosed in the developed world annually [(1)]. Pathologists currently use the World Health Organization (WHO) modification of the Revised European-American Lymphoma (REAL) classification for the histologic classification for adult Hodgkin lymphoma HL [(2, 3)], (WHO/REAL classification):

- **Classical HL:** Nodular sclerosis NS, Mixed-cellularity MC, Lymphocyte depletion LDHL & Lymphocyte Predominance classical LPHL.
- **Nodular lymphocyte–predominant HL:** The REAL Classification of Lymphoid Neoplasm's proposed separating nodular lymphocyte–predominant HL (CD15-, CD20+, CD30-) from lymphocyte-rich classical HL (CD15+, CD20-, CD30+), on the basis of these immunophenotypic differences [(3,4)]. HL has bimodal age distribution with most patients diagnosed between 15and 30 years of age, followed by another peak in adults over the age of 50. HL is usually confined to the lymph nodes Cervical and mediastinal lymph nodes are the most common site of lymph nodal involvement in HL. Isolated infra diaphragmatic lymphadenopathy occurs in less than 10 % of patients at diagnosis [(5)]. Extra nodal involvement is less common in HL than in NHL and seen in only 10 –15 % of patients. The most frequent sites of extra nodal involvement are bone, bone marrow, lung and liver [(6)].

Clinical staging system that divides patients into four major groups: Early-stage favorable (stage I–II with no unfavorable factors), ***early -stage unfavorable*** I – II with any of the unfavorable factors), ***advanced favorable*** (clinical stage III or IV with zero to three adverse risk factors listed below) and ***advanced unfavorable*** (clinical stage III or IV with four or more adverse risk factors listed below). Assessment of prognosis is important for formulating management strategies. Large mediastinal adenopathy (>33 % of the thoracic width on the chest x-ray or CT), presence of B symptoms, more than 2 or 3 nodal sites of disease or an ESR of 50 or more are unfavorable prognostic factors for patients with stage I and II disease. For patients with advanced-stage HL, the International Prognostic Factors Project has developed an International Prognostic Index with a prognostic score that is based on the following seven adverse factors: age more than 45 years, male gender, stage IV disease, albumin level below 4.0 g /dl, hemoglobin level below 10.5 g/dl, white blood cell count more than 15,000/mm³, absolute lymphocytic count less than 600 mm³ or a lymphocyte count less than 8 % of the total WBC count [(7)].

HL is a highly chemo sensitive disease, with a remarkable remission rate of higher than 75% in patients undergoing standard ABVD treatment (doxorubicin, bleomycin, vinblastine, and dacarbazine).

In patients with advanced-stage or unfavorable limited-stage HL, however, the management approach has shifted toward early therapy intensification to overcome chemotherapy resistance and afford a long-term survival. The ongoing prospective interim PET–adapted trials will probably answer the questions centered on whether a PET-adapted approach will allow clinicians to lower the intensity of both

chemotherapy and radiotherapy schedules with sufficient safety margins and the effectiveness of escalation protocols. Despite excellent survival rates achieved by most HL patients, 10%–15% of early-stage and 20%–30% of advanced-stage patients ultimately succumb to progression because of chemo resistant or refractory disease [8]

Most patients with limited-stage disease that is, almost a third of patients diagnosed with HL [9].can be cured. The current trend in this population is to optimize the efficacy of treatment with the least toxicity. The realization of significant long-term chemotherapy- and radiotherapy-related adverse effects, including second neoplasm's (25-y actuarial risk of death, 13.5%), cardiovascular disease (6.9%), and infertility (60%–91% with escalated therapy depending on the number of treatment courses), paved the way to clinical trials with less intensive treatment protocols[10-13]. The interest in decreasing first-line therapy in limited-stage favorable HL (non bulky, stage I–IIA) has further grown in light of prior reports of acceptable overall survivals, without compromised overall survivals, using abbreviated therapies. In randomized reduced-treatment-intensity trial on patients with early-stage, favorable HL, treatment with 2 cycles of ABVD followed by 20 Gy of involved-field radiation therapy (IFRT) was as effective as, and less toxic than, 4 cycles of ABVD with 30 Gy of IFRT[14]. However, intensified treatments for such patients should be tempered by the awareness of significantly increased toxicity and the paucity of data to prove a survival benefit. Thus, therapy optimization presently includes elimination of radiation and abbreviation of therapy cycles in a subgroup selected with a PET-directed approach.

Primary resistance is generally considered, in itself to be a poor prognostic marker [15-17].

However no patients with primary resistant disease survive more than 8 years using conventional chemotherapy alone (0-8%),while the projected 20 -year survivals for those with early relapse (<12 months from primary therapy) or late relapse (>12 months from primary therapy) were previously estimated to be 11% and 22% respectively, in the era of less intensive induction regimens[15,16].

Other factors found to have prognostic significance in some but not all studies include extra nodal disease [18] and the presence of B symptoms. Using a 3 point scale based on: 1)- early relapse or primary refractory disease 2)-extra nodal disease, and 3)- presence of B symptoms at relapse, patients could be stratified with 5-year EFS of only 27% and 10% in those with a score of 2 or 3 respectively [17].

Although there have been many phase II studies reporting results using salvage regimens for relapsed or refractory HL, there are no randomized trials and no consensus on the most effective second-line chemotherapy regimen, however salvage chemo-therapy followed by autologous stem cell transplantation (ASCT is the treatment of choice in patients with relapsed HL or if the disease is refractory to initial chemotherapy [19, 20].

2. Material and methods:

Fifty eight patients with pathologically proven HL were studied during the period (2000 -2014). Immunophenotyping using (CD15+, CD20-, CD30+, CD45) to differentiate different subtypes.

Eligibility criteria required that patients be ≥15 years of age and have an Eastern Cooperative Oncology Group performance status of 0–2. At least one site of bi-dimensionally measurable tumor as assessed by clinical examination, computed tomography (CT) or PET CT had to be identified. Additional eligibility criteria included: normal bone marrow function absolute neutrophil count >1.5 × 10 l, platelets >100 × 10 serum creatinine <140 m mol/l, serum aspartate or alanine aminotransferase <2.5 × upper limit of normal (ULN); and bilirubin <1.5 × ULN **Exclusion criteria**: pregnancy or a serious intercurrent illness or medical condition such as active uncontrolled infection or significant cardiac dysfunction that would preclude safe administration of the protocol treatment. Prior treatment with gemcitabine, cisplatin or high-dose chemotherapy and stem cell trans-plantation was also an exclusion criterion.

All patients were staged according to Ann Arbor staging system according to the history, clinical examination, CT findings. Patients included in the study performed CT or PET CT for initial staging, after the first course of chemotherapy (4–6 weeks) and after the end of treatment. First line Treatment was ABVD (adriamycin, bleomycin, vinblastine & dacarbazine) in standard doses every 2 weeks with dose modification, granulocyte stimulation, or delays depending on blood counts with or without local radiotherapy. Response of treatment was assessed according to the International Project Criteria for Assessment of Response to Therapy for Lymphoma. Relapsed or refractory patients to treatment were randomized into second line **Group A**: GDP chemotherapy consisted of (gemcitabine 1000 mg/m2 intravenously (IV) on days 1 and 8, dexamethasone 40 mg IV on day 1, 40 mg orally on days 2–4, and cisplatin 75 mg/m2 IV on day 1). GDP was administered every 21 days in an outpatient setting. **Group B**: DHAP: (dexamethasone 40 mg days 1–4, cytarabine 2 g/m2 every 12 hours x 2 on day 2, cisplatin 100 mg/m2/24 hours on day 1), response to first and second line treatment and correlation to PFS were recorded informed written consents were taken.

Statistical methods:

The primary end-point of this study was the overall response rate (complete remission + partial remission) to primary and second line treatment, and correlation with progression free survival. Secondary end-points were progression-free and overall survival. Survival calculations were estimated using the Kaplan-Meier method Data were analyzed with SPSS Statistics 16.0 software.

3. Results:

Fifty eight patients with pathologically proven HL were studied during the period (2000 -2014), range of age was (15-85 years), mean age was 37.7 years, 71 % < 45 years & 29% ≥ 45 years, with nearly equal sex affection. The most common histological subtype was nodular scelerosing NS in 43% of patients, followed by mixed cellularity MC in 31% of patients and Lymphocyte-predominant Hodgkin lymphoma LPHL in 26% of patients. 57% was stage III, 24% stage II, and 19% was stage I .62% were a symptomatic, and 38% presented with B symptoms. 83% received ABVD, and 17% received ABVD +IFRT as a first line of treatment. Response to first line complete response in 65.5% of patients, partial response in 19% of patients (RR was 84.5%), while 15.5% of patients was refractory **(table 1)**. Mean overall survival was 3.97 ± 0.33 years **(figure 1)**. Mean progression free survival was 2.77 ± 0.27 years **(figure 2)**. There was a significant relation of response to first line treatment and PFS (P-value was 0.039*) **(table 2 & figure 3)**.

Relapsed and refractory patients were (40%) of patients were randomized into two groups; group A received CISP + GEMZ in 21% of patients, and group B received DHAP in 19% of patients. The main pathological subtype was NS in 52.2% of patients followed by MC in 39% of patients & LPHL in 9% of patients. 39% of patients was high risk, 52% of patients was intermediate risk and 9% of patients was standard risk. Response to second line treatment in **group A**: CR in 25% of patients while in **group B** CR in 27% of patients, (RR to second line treatment was 67% in group A and 64% in group B). Mean PFS in **group A** was (2.53 ± 0.56) while in **group** B was (1.68 ± 0.19) **(Table 3)**, with a non-significant difference. (P-value was 0.096) **(Figure 4)**. As regard treatment toxicity in group B: Grade 3/4 nutopenia in (82%) of patients, vomiting in (27%) of patients and TCP in (64%) of patients while, in group A: Grade 3/4 neutropenia in (8%), vomiting in (17%) & TCP in (17%) of patients respectively.

Table (1): Patients characteristics

	No. (n= 58)	%
Age:		
< 45 years	41	70.7
≥ 45 years	17	29.3
Mean ± SD (Range)	37.71 ± 19.24 (15.0 – 85.0)	
Sex:		
Male	30	51.7
Female	28	48.3
Sub-type:		
LPHL	15	25.9
MC	18	31.0
NS	25	43.1
Stage:		
Stage I	11	19.0
Stage II	14	24.1
Stage III	33	56.9
Sub-stage:		
Stage A	36	62.1
Stage B	22	37.9
First line of treatment:		
ABVD	48	82.8
ABVD+IFRT	10	17.2
Response rate to first line:		
RR	49	84.5
Second line of treatment:		
Group A	12	20.7
Group B:	11	19.0
Response Rate to second line		
Group A	8/12	67
Group B	7/11	73

Table (2): progression free Survival according to first line response

Response	Mean ± SE	Median	*P*-value
Complete response	3.16 ± 0.37	2.5	0.039*
Partial response	1.99 ± 0.27	2.0	
Refractory disease	2.08 ± 0.56	1.5	

Table (3): progression free Survival according to second line

Second line treatment	Mean ± SE	Median	*P*-value
CISP+GEMZ	2.53 ± 0.56	2.0	0.096
DHAP	1.68 ± 0.19	2.0	

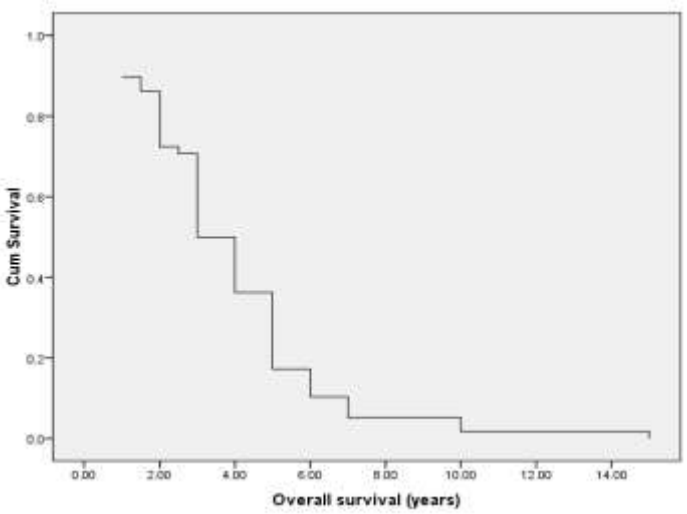

Figure (1): Overall survival (mean 3.97 ± 0.33)

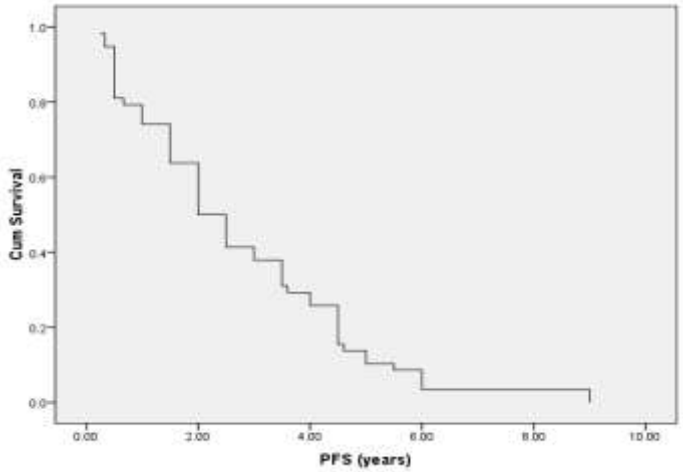

Figure (2): Progression free survival (mean 2.77 ± 0.27)

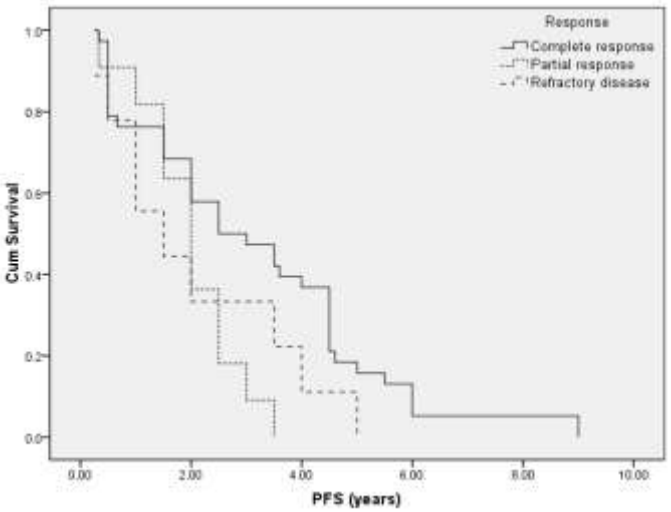

Figure (3): Progression free survival according to response to first line

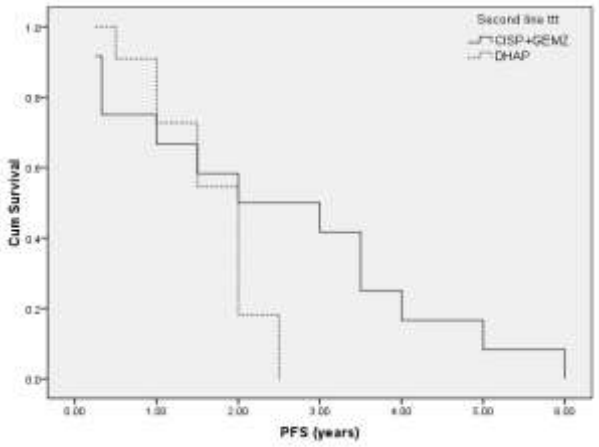

Figure (4): Progression free survival according to second line treatment

4. Discussion:

The majority of patients with Hodgkin's disease will be cured with primary treatment; ABVD is the standard treatment for patients with newly diagnosed Advanced stage Hodgkin's disease. Analysis of the data of the patients received first line treatment show that: 17% of patients received ABVD+IFRT and 83% of patients received ABVD, with a high response rate 84.5% and acceptable (refractory 15.5% & relapse rate 24.5%) with a significant correlation of response to first line treatment and PFS (P-value was 0.039*).

This results agree with the current trend to optimize the efficacy of treatment with the least toxicity based on the realization of significant long-term chemotherapy and radiotherapy-related adverse effects [10-13] and early therapy intensification to overcome chemotherapy resistance and afford a long-term survival In patients with advanced-stage or unfavorable limited-stage HL.

Based on single-agent activity of gemcitabine in Hodgkin's disease, we choose to evaluate this agent in combination with cisplatin and dexamethasone in patients with Hodgkin's disease who required second-line therapy. The addition of cisplatin to gemcitabine was based on the observation of synergy between the two drugs in vitro [21] and the high RR and manageable hematological and non-hematological toxicity of this combination in patients with solid tumors [22, 23]. Relapsed and refractory patients in our study were 40%; they were randomized into two groups, group A received CISP+GEMZ in 21% of patients, group B received DHAP in 19% of patients.

Response Rate to second line treatment **was** higher in group A **than** in group B**.** while treatment toxicity was lower in group A than in group B. The CR in our study demonstrates that GDP compares favorably with other published salvage regimens while RR still lower than Dexa-BEAM, ICE and MINE (Table 4). As the patients evaluated in these trials probably have differing prognostic features; randomized trials are required in the future to permit a direct comparison of the efficacy and toxicities of the different salvage regimens**.**

Conclusion:

This study demonstrates that GDP is an active outpatient treatment with a higher RR and limited treatment toxicity in comparison to DHAP for patients relapsed or refractory Hodgkin's disease who are unfit for autologous stem cell transplantation.

Table (4): results of different salvage regimens in relapsed and refractory HL

Chemotherapy regimen	**No. of patients**	**CR (%),**	**RR (%),**
Dexa-BEAM [24]	144	27	81
ICE [25]	65	26	85
MINE [26]	157	-	75
GDP	12	25	67
DHAP	11	27	64

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