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Outcome of Second Line Chemotherapy (Gemcitabine, Dexamethasone, and Cisplatin) in Relapsed and Refractory Non Hodgkin Lymphoma

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Abstract

Background: The treatment of patients with relapsed or refractory non-Hodgkin lymphoma remains challenging. The strategy for management of relapsed or refractory disease is to deliver salvage chemotherapy, followed by autologous stem-cell transplantation in responding patient. Such salvage therapies typically consist of cytotoxic agents that have not been used in first line therapy.

Aim of Study: In this study we are trying to study one of the salvage chemotherapy lines which is GDP regarding response rate, quality of life and toxicity.

Patients and Methods: Seventy patients diagnosed as refractory or relapsed NHL were included in the study; all patients received GDP for 4 to 6 cycles. Primary end point was to evaluate overall response to treatment; secondary end point was to evaluate quality of life and toxicity. An informed written consent was obtained from all the patients and approval of Research Ethics Committee of Assiut, Faculty of Medicine was obtained prior to the study.

Results: The overall response was 65% with complete response 25% and partial response 40%. Regarding quality of life it was noticed that 32.9% patients using GDP were improved, 40% were stable patients while significant deterioration occurred in 27.1%. Regarding toxicity profile, occurrence of neutropenia was 50% with grade III-IV 15%, thrombocytopenia 40% with grade IV-V 5%, anemia 60% with grade II-III 7%. Nausea 50% with grade III-IV 3%, vomiting 40% with grade III-IV 10%, diarrhea 34.3% with grade II-III 5%. Renal toxicity 31.4% with grade I-II 15%, neurological toxicity 40% grade I-II 10%. Hepatic toxicity 25.7% with grade I-II 20%.

Conclusion: GDP is effective as second line chemotherapy with good response rate, quality of life and a manageable range of toxicity.

Key Words: *GDP – NHL – Relapsed – Refractory lymphoma.*

Declaration: *No conflict of interest.*

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Introduction

NON-HODGKIN Lymphomas (NHLs) are a heterogeneous group of neoplasm of the lymphatic system [1] that results from an uncontrollable proliferation of B or T lymphoid cells and Natural Killer (NK) cells [2].

Histologic type and stage are the main factors that treatment depends on in patients with NHL [3], in patients with invasive NHL; there are still reports of 50-60% of experience drug recurrence after the first-line treatment.

Patients are categorized depending on response to frontline chemotherapy as having primary refractory disease (failure to have a Complete Response (CR), progression or transient response upon frontline therapy, CR/Partial Response (PR) lasting $^{<3}$ months), early relapse (CR lasting <12 months) and late relapse (CR lasting >12 months) [4].

The treatment strategy for relapsed or refractory lymphoma is to deliver salvage chemotherapy, followed by autologous stem-cell transplantation in responsive patients [5].

The choice of salvage therapy is still debated; several second-line chemotherapy regimens-which are designed to increase the number of patients eligible for transplantation through the use of more intense chemotherapy-have been evaluated and were discovered to have considerable hematologic toxicity and use of health care resources [6].

Those salvage chemotherapies consist of cytotoxic drugs that have not been used in first line therapy.

Gemcitabine is a cytidine analog that has the advantages of more rapid uptake by cells, more efficient phosphorylation, wide spectrum of anti-tumor activity and slower elimination [7].

In our study we tried to study one of the second lines of chemotherapy which is Gemcitabine, Dexamethasone, and Cisplatin (GDP) regarding response rate, toxicity and quality of life.

Patients and Methods

This prospective study was conducted at Clinical Hematology Unit in Internal Medicine Department and Medical Oncology Department, Assiut University Hospitals during 2015-2016, the study included 70 patients diagnosed as refractory or relapsed NHL, and the patients received Gemcitabine, Dexamethasone and Cisplatin (GDP) for 4 to 6 cycles.

Those patients received GDP:

- Gemcitabine 1,000mg/m^2 i.v. on days 1 and 8.
- Dexamethasone 40mg i.v. on days 1-4.
- Cisplatin 75mg/m^2 i.v. on day 1, every 21 days for 4 to 6 cycles.

All studied patients were subjected to full history taking, complete physical examination, laboratory investigations including complete blood count with differential count, liver function test, kidney function test and lactate dehydrogenase level, excisional lymph node biopsy with immunophenotyping to diagnose B or T cell type, multislice CT chest and abdomen for disease assessment, bone marrow aspirate and biopsy, international prognostic index calculation.

Re-evaluation of the patients regarding response according to Lugano response criteria for NHL after second, fourth and six cycles. Toxicity was evaluated after second, fourth and six cycles according to the Common Toxicity Criteria of the National Cancer Institute [8].

Quality of Life (QoL) assessment was done using the Functional Assessment of Cancer Therapy (FACT) instrument [9] which considers a change of 10% or more compared to baseline quality of life a meaningful change and classified into improved, stable and worse.

Statistical analysis:

The results of the study were tabulated and statistical analysis was carried out using statistical package for Social Science SPSS Version 20, using significant level (p<0.05). Chi square test was used to compare frequencies.

Results

The study included 70 patients, 42 males (60%) and 28 females (40%) with age ranged from 28 to 54 years, 43 patients (61.4%) were diagnosed as B cell lymphoma and 27 patients (38.6%) as T cell lymphoma, constitutional symptoms were present in 47 patients (67.1%) and were absent in 23 patients (32.9%), according to response to previous treatment, 22 patients were refractory; 35 patients with relapse <1 year and 13 patients with relapse >1 year. IPI risk factor at study entry was low and low-intermediate risk was detected in 44 patients (62.9%), high-intermediate risk was detected in 20 patients (28.6%) and high risk was detected in 6 patients (8.6%) (Table 1).

Table (1): Characteristics of patients included in the study.

Variables	Number
Age (years):	
Median (range)	51 (28-54)
Sex:	
Male	42 (60%)
Female	28 (40%)
Constitutional symptoms:	
Present	47 (67.1%)
Absent	23 (32.9%)
IPI risk factors at the entry:	
Low, low-intermediate risk	44 (62.9%)
High-intermediate risk	20 (28.6%)
High risk	6 (8.6%)
Histological type:	
B-cell	43 (61.4%)
T-cell	27 (38.6%)
Response to previous therapy:	
Refractory	22 (31.4%)
Relapse $^{<1}$ year	35 (50%)
Relapse >1 year	13 (18.6%)

It was noticed that age, sex, presence of constitutional symptoms, response to previous therapy and histological type had no effect on response or toxicity.

Regarding the International Prognostic Index; 6 (8.6%) patients were high risk while majority of patients (62.9%) were low and low-intermediate.

Over all response was observed in 46 patients (65%). Complete response was observed in 18 patients (25%) patients, partial response was observed in 28 patients (40%) (Table 2).

Table (2): Overall response rate.

	(n=70)
Intention to treat population:	70/70
Overall response rate	46 (65%)
Partial response	28 (40%)
Complete response	18 (25%)

Characteristics of patients who enter into complete response were; age group between 29 and 45 years, B symptoms were positive, IPI index was low and low-intermediate, previous treatment was RTH and Anthracycline, early relapse was 20% and late relapse was 50% (Table 3).

Characteristics of patients who enter into partial response were; age group between 30 and 60 years, B symptoms were positive, IPI index was low-intermediate, high-intermediate and high risk, previous treatment was RTH and Anthracycline, early relapse was 40% and late relapse was 25% (Table 3).

Table (3): Details of patients who enter in complete and partial response.

	Age	B symptoms	IPI index	Previous TT	Early relapse	Late relapse
Complete response	29-45	+ve	Low, low-intermediate	RTH Anthracycline	20%	50%
Partial response	30-60	+ve	High-intermediate Low-intermediate & high risk	RTH Anthracycline	40%	25%

According to the type of lymphoma overall response was observed in 34 (80%) and 18 (68%) patients in B-cell and T-cell subtypes respectively (Table 4).

Table (4): Overall response based on types of lymphoma.

	B-cell (n=43)	T-cell (n=27)
Overall response	34 (80)	18 (68)

Those patients who relapsed after previous therapy had higher frequency of response to the second line than those who were refractory to previous therapy 40 (83.33%) vs. 13 (57.1%) patients (Table 5).

Table (5): Overall response based on response to previous therapy.

	Relapse (n=48)	Refractory (n=22)
Overall response	40 (83.33)	13 (57.1)

The event of interest was death of the patients during the duration of the study whether improved or not and other cases were considered censored (Table 6).

Table (6): Summary of cases according to survival analysis.

	Number of event	Number of censored
GDP regimen	9 (12.86)	61 (87.14)

It was noticed that occurrence of neutropenia, nausea, vomiting, diarrhea, and hepatic toxicity are the main side effects, neutropenia 50% with grade III-IV 15%, thrombocytopenia 40% with grade IV-V 5%, anemia 60% with grade II-III 7%. Nausea 50% with grade III-IV 3%, vomiting 40% with grade III-IV 10%, diarrhea 34.3% with grade II-III 5%. Renal toxicity 31.4% with grade I-II 15%, neurological toxicity 40% grade I-II 10%. Hepatic toxicity 25.7% with grade I-II 20% (Table 7).

Table (7): Adverse effects of both regimens.

Variables	(n=70)
Hematological adverse effects:	
Anemia	30 (60%)
Grade II-III	7%
Neutropenia	35 (50%)
Grade III-IV	15%
Thrombocytopenia	28 (40%)
Grade IV-V	5%
Gastrointestinal effects:	
Nausea	35 (50%)
Grade III-IV	3%
Vomiting	28 (40%)
Grade III-IV	10%
Diarrhea	24 (34.3%)
Grade II-III	5%
Renal toxicity:	22 (3 1.4%)
Grade I-II	15%
Neurological toxicity:	28 (40%)
Grade I-II	10%
Hepatic toxicity:	18 (25.7%)
Grade I-II	20%

It was noticed that 23 patients (32.9%) were improved, stable patients were 28 (40%) while significant deterioration occurred in 19 patients (27.1%) (Table 8).

Table (8): Quality of life assessment.

	(n=70)
QoL assessment:	
Improved	23 (32.9)
Stable	28 (40)
Worse	19 (27.1)

No follow-up was done for the patients after entery into the response was detected as this was the end point of the study.

Discussion

Refractory non-Hodgkin lymphoma is that lymphoma that hasn't responded to initial treatment, progressive or has a transient response to treatment, relapsed non-Hodgkin lymphoma is NHL that responded to treatment but then returns, relapse may occur several months to years after the initial remission.

Patients with aggressive lymphoma, refractory or relapsed after frontline chemotherapy experience superior overall survival when treated with high-dose chemotherapy with stem-cell transplantation for chemo sensitive patients [10].

In this study we tried to study one of the salvage chemotherapy lines which is GDP regarding response rate, quality of life and toxicity.

The current study included 70 patients received GDP regimen. Regarding response rate, in the current study over all response were observed in 46 patients (65%), complete response was 25% and partial response was 40%, those results were similar to a study by Ismaeil, et al., [11] which include sixty two patients with histological diagnosis of relapsed or refractory DLBCL 43 males and 19 females, with a median age 48 years (range 19-63) received GDP or DHAP-it was reported that overall response rate was 65%, 29% complete response and 38% partial response in GDP group, those similar response rates may be due to similar patient inclusion criteria.

In another study by Fei Qi, et al., [13]-in which twenty-five patients were reviewed with relapsed or refractory PTCL-NOS, median age was 50 years (range 14-72 years), all patients received GDP regimen as second-or third-line chemotherapy-revealed that overall response was observed in 16 patients (64.0%), complete response was observed in 4 patients (16%) and partial response was 11 patients (44%).

Also another study by Ghio, et al., [10]-from February 2006 to July 2014, 45 relapsed/refractory DLBCLs patients treated with GDP-R, eligibility criteria were men or women aged >18 years-reported that overall response rate was 48.8%, complete response 15/45 (33.3%) and partial response 7/45 (15.5%), those different response rates may be due to higher percentage of high risk patients on the study.

There was significant difference in the overall response according to response to the previous therapy where those patients who were relapsed after previous therapy had higher frequency of response to the second line than those who were refractory to previous therapy 30 (83.33%) vs. 48 (57.1%) patients.

In a study by Ismaeil, et al., [11] it reported that better response was observed in patients who had complete response after the previous chemotherapy.

Regarding toxicity, in the current study it was noticed that occurrence of neutropenia was 35 (50%), this finding also in agreement with Ismaeil, et al., [11] that reported that neutropenia was 62.9% in patients.

And in contrast with another study by Crump M, et al., [12]-which include 619 patients with relapsed/refractory aggressive lymphoma randomly assigned to treatment with GDP or DHAP-by it was noticed that Grade 3 or 4 adverse events were observed significantly less frequently during the first two cycles of chemotherapy among patients receiving GDP (47%).

In the current study it was noticed that occurrence of hepatic toxicity was 18 (25.7%), this finding was in agreement with a study by Fei Qi, et al., [13] which noticed that seven patients (26.0%) had liver dysfunction indicated by moderately elevated alanine aminotransferase and aspartate aminotransferase in serum.

In the current study it was reported that occurrence of other adverse effects as renal was 31.4% and neurological was 40%, those finding were in contrast to a study by Ismaeil, et al., [11] that reported that renal toxicity occur in 76% and neurological toxicity in 60%.

In the current study it was reported occurrence of thrombocytopenia was 40 %, this finding was in agreement with a study by Crump M., et al., [12] reported that patients allocated to GDP required fewer platelet transfusions (31 %).

QoL assessment using Functional Assessment of Cancer Therapy (FACT-Total) scores showed that 23 (32.9%) patients using GDP were improved,

stable patients were 28 (40%) while more significant deterioration was occurred in19 (27.1%) patients, this finding was in agreement with Crump, et al., **[12]** that showed that, compared with baseline status, there was less deterioration among patients who were allocated to GDP, also more patients receiving GDP had an improved clinically meaningful change score (18%) in patients received GDP and fewer had a worse clinically meaningful change score (33%), also fewer patients receiving GDP required hospitalization (47%).

Recommendation:

Our study recommends that is for patients who are in need to receive GDP to be early age group, with less co morbidities so they can overcome the toxicities that result from receiving the treatment.

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نتائج الخط العلاجى الكيميائى الثانى (جيمسيتابين، ديكساميثازون وسيسبلاتين) فى مرضى سرطان الغدد الليمفاوية الغير هودجيكينيه المنتكسين والغير مستجيبين للعلاج

سرطان الغدد الليمفاوية الغير هودجيكينيه هو مجموعة غير متجانسة من الأورام فى الجهاز اللمفاوى والتى تنتج عن إنتشار لا يمكن السيطرة عليها من الخلايا الليمفاوية البائية أو التائيه والخلايا القاتلة الطبيعية.

النوع النسجى والمرحلة هم العوامل الرئيسية التى يعتمد عليها العلاج فى المرضى الذين يعانون سرطان الغدد الليمفاوية الغير هودجيكينيه، فى هؤلاء المرضى لا تزال هناك تقارير بأن ٥٠–٦٠٪ من المرضى يخضعون لتجربة تكرار الخط العلاجى الكيميائى الثانى بعد الخط العلاجى الأول.

إستراتيجية العلاج فى مرضى سرطان الغدد الليمفاوية الغير هودجيكينيه المنتكسين والغير مستجيبين للعلاج هو تقديم علاج كيميائى إنقاذى، تليها زرع الخلايا الجذعية الذاتية فى المرضى المستجيبين للعلاج.

وتتكون هذه العلاجات الكيميائية من العلاجات التى لم تستخدم فى الخط الكيميائى الأول.

ويتميز جيمسيتابين بأن له إمتصاص أكثر سرعة من قبل الخلايا وبطء فى التخلص منه، أكثر فعالية الفسفرة ومجموعة واسعة من النشاط.

فى دراستنا هذه حاولنا دراسة واحدة من الخطوط الثانية من العلاج الكيميائى الذى هو جيمسيتابين، ديكساميثازون، وسيسبلاتين فيما يتعلق معدل الإستجابة، السمية وكفاءة الحياة.

الهدف من الدراسة: النقطة النهاية الأولية هى تقييم الإستجابة الشاملة للعلاج والنقطة النهاية الثانوية هى تقييم كفاءة الحياة بعد تلقى العلاج والسمية الناتجة عنه.

نتيجة الدراسة: أجريت هذه الدراسة الإستطلاعية فى وحدة أمراض الدم السريرية فى قسم الطب الباطنى وقسم الأورام الطبى فى مستشفيات جامعة أسيوط خلال الفترة ٢٠١٥–٢٠١٦، وشملت الدراسة ٧٠ مريضا تم تشخيصهم على إنهم غير مستجيبين للعلاج أو منتكسين، وتلقى المرضى جيمسيتابين، ديكساميثازون وسيسبلاتين لمدة ٤ إلى ٦ دورات.

وكانت الإستجابة الإجمالية ٦٥٪ مع إستجابة كاملة ٢٥٪ والإستجابة الجزئية ٤٠٪. أما فيما يتعلق بنوعية الحياة فقط لوحظ تحسن نسبة المرضى بنسبة ٣٢.٩٪، و٤٠٪ من المرضى مستقرين، بينما حدث تدهور كبير فى ٢٧.١٪. فيما يتعلق بسمية السمية، كان حدوث نقص فى كرات الدم البيضاء ٥٠٪ مع الصف الثالث والرابع ١٥٪، قلة الصفيحات ٤٠٪ مع الصف الرابع–الخامس ٥٪، وفقر الدم ٦٠٪ مع الصف الثانى والثالث ٧٪. الغثيان ٥٠٪ مع الصف الثالث والرابع ٣٪ والقئ ٤٠٪ مع الصف الثالث والرابع ١٠٪ والإسهال ٣٤.٣٪ مع الصف الثانى والثالث ٥٪ سمية الكلى ٣١.٤٪ مع الصف الأول والثانى ١٥٪، والسمية العصبية ٤٠٪ مع الصف الأول والثانى ١٠٪، السمية الكبدية ٢٥.٧٪ مع الصف الأول والثانى ٢٠٪.