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Efficacy and toxicity of gemcitabine/ dexamethasone / carboplatin versus ESHAP protocol in treatment of relapsed/ refractory Non-Hodgkin's lymphomas (NHL)

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Abstract:

Sensitivitytosalvage chemotherapy is one of the strongest predictors of OS and PFS after high-dose therapy with autologous bone marrow or peripheral blood stem cell transplantation (ABMT) in relapsed or refractory non-Hodgkin'slymphoma. Consequently, efforts have been focused on developing salvage chemotherapy protocols aiming at improving response rate for this particular group of patients. (6). Response rates to conventional chemotherapy are generally greater than 50%; however, Most NHL patients eventually relapse. Relapse of NHL may occur several months to years after the initial remission; however, the majority of relapses for aggressive patients.

Numerous salvage chemotherapy regimens have been used to treat relapsed or refractory DLBCL.The majority are based on agents that demonstrate non cross resistance to those used in primary therapy. Studies on salvage therapy have generally included all patients with aggressive lymphoma and are not restricted to DLBCtechniques(5). An ideal salvage therapy regimen for use prior to ASCT should have a high response rate, low hematologic, andnonhematologictoxicity.(3)

Keywords Relapsed or refractory NHL, salvage chemotherapy regimens, High-dose therapy with Autologous stem cell transplantation (ASCT), Gem /dexa/Carbo, ESHAP, response rate and Toxicity.

1. Introduction:

Treatment of relapsed aggressive NHL may consist of chemotherapy,high-dose chemotherapy with stem cell transplantation, targeted therapy, or acombination of these treatment techniques. Multi-modality treatment, which utilizes two or more treatment techniques, is increasingly recognized as an important approach for improving a patient's chance of cure or prolonging survival.(7)

Circumstances unique to each patient's situation may influence how these general treatment principles are applied. The potential benefits of multi-modality care, participation in a clinical trial, or standard treatment must be carefully balanced with the potential risks. (8)

In DLBCL ASCT has become the standard of care for patients in first relapse. Based on the landmark Parma trial, This study included 215 chemotherapy- sensitive relapsed DLBCL patients were enrolled . After an initial two cycles of DHAP (dexamethasone, cisplatin, cytarabine) 109 patients (50 percent) were randomly assigned to receive either four additional cycles of DHAP or high-dose chemotherapy followed by autologous transplant Both EFS and OS were significantly superior in the transplantation group compared with the chemotherapy alone group (46% and 53% vs 12% and 32%, respectively). (2)

Aim of the work:

This study was conducted for assesment of efficacy and toxicity ofgemcitabine/dexamethasone/Carboplat in versus ESHAP protocol assalvage second line chemotherapy in treatment of relapsed/ refractory Non-Hodgkin's lymphomas (NHL) patients .

2. Patients and Methods:

This is aprospective randomized study including patients with relapsed and refractory aggressive NHL who presented to BENI SUEF university hospital and BENI SUEF insurance hospital between October 2016 and December 2018. The trial was approved by the institutional research committee . atotal of 42 patients were included, randomly assigned as follow: 22 patients in Carbo/Gem/dexa arm and 20 patients in ESHAP arm.

Study endpoints:

The primary end point was the response rate (complete remission + partial remission) of gemcitabene/dexamethasone/carboplatin e versus ESHAP protocol drugs as salvage second line chemotherapy regimen while secondary end points were time to disease progression, overall survival and chemotherapy toxicity of both arms.

Treatment protocol:

Eligible patients were randomly assigned to gem/dexa/ carbo versus ESHAP protocol, in first arm patients recieved Gemcitabine 1000mg/m2 IV Day 1 and 8 in 250 ml sodium chloride 0.9% over 30 minutes, carboplatin AUC 5 and dexamethathone 40 mg daily days 1–4 ,treatment will be repeated every3weeks with Premedications, ondansetron 8-16 mg intravenous and Proton pump inhibitor intravenous 40 mg prior to chemotherapy and Dexamethasone 8mg intravenous prior to chemotherapy D1+2 and 2 days after chemotherapy daily for 1week.

In the second arm patients recieved Etoposide 40 mg/m2 IV Days 1 to 4 IV infusion over 60 minutes in 500 ml sodium chloride,Methylprednisolone 500 mg IV Days 1 to 4 IV infusion in 100 ml sodium chloride 0.9% over 30 minutes,Cytarabine 2000 mg/m2 IV Day 5 1V infusion in 500 ml sodium chloride 0.9% over 2 hours and Cisplatin 25 mg/m2 IV Days 1 to 4 IV infusion in 500ml sodium chloride 0.9% over 22 hours, with Premedications Premedications, ondansetron 8-16 mg intravenous D1-5 and Proton pump inhibitor intravenous 40 mg prior to chemotherapy D1-5 and Dexamethasone 8mg intravenous prior to chemotherapy D1-5 and 2 days after chemotherapy daily for 1week and 20 mmol magnesium sulphate + 20 mmol potassium chloride on 1000ml Sodium chloride 0.9% + D1-5 (ensure that urine output >100ml/hour) Cycle repeated every 28 days

Statistical analysis:

The mean Gem/Carbo/dexa group's and ESHAP group's age were 54.6 and 49 years ranged from 32 and 26 years to 61 and 64 years with median 57 and 53 years for both groups respectively. There were 16(72.7%) and 10(50%) males and 6(27.2%) and

10(50%)femalesinGem/Carbo/dexa group and ESHAP group respectively,4patients(18.2%)inGem/Carbo/dexa arm and 2 patients (10%) in and ESHAP arms were diabetics, regarding HCV infection in Gem/Carbo/dexa group and ESHAP group there were 4(18.2%) and 4(20%) with HCV positive for both arms respectively with no statistical significant difference between them regarding general patient characteristics (P-value=0.697).

There were no statistical significant differences between both groups regarding disease characters at relapse including pathology, original IPI, largest tumor diameter, stage, B symptoms, disease status(relapsedversusrefractory),extranodal involvement, Bone marrow infilteration ,performance status and age adjusted IPI (P-value>0.05) and LDH. regarding to pathology there were 20 cases DLBCL with 2 cases mantle cell lymphoma in Gem/dexa /Carbo arm, in ESHAP arm there were 19 cases DLBCL with 1 case Tcell lymphoma.

The total number of cycles received was 82 cycles in Gem/Carbo/dexa arm and 70 cycles in ESHAP arm with the Median number of cycles was 6 cycles ranged (3-8) in Gem/Carbo/dexa arm and 4 cycles ranged (2-6) in ESHAP arm.

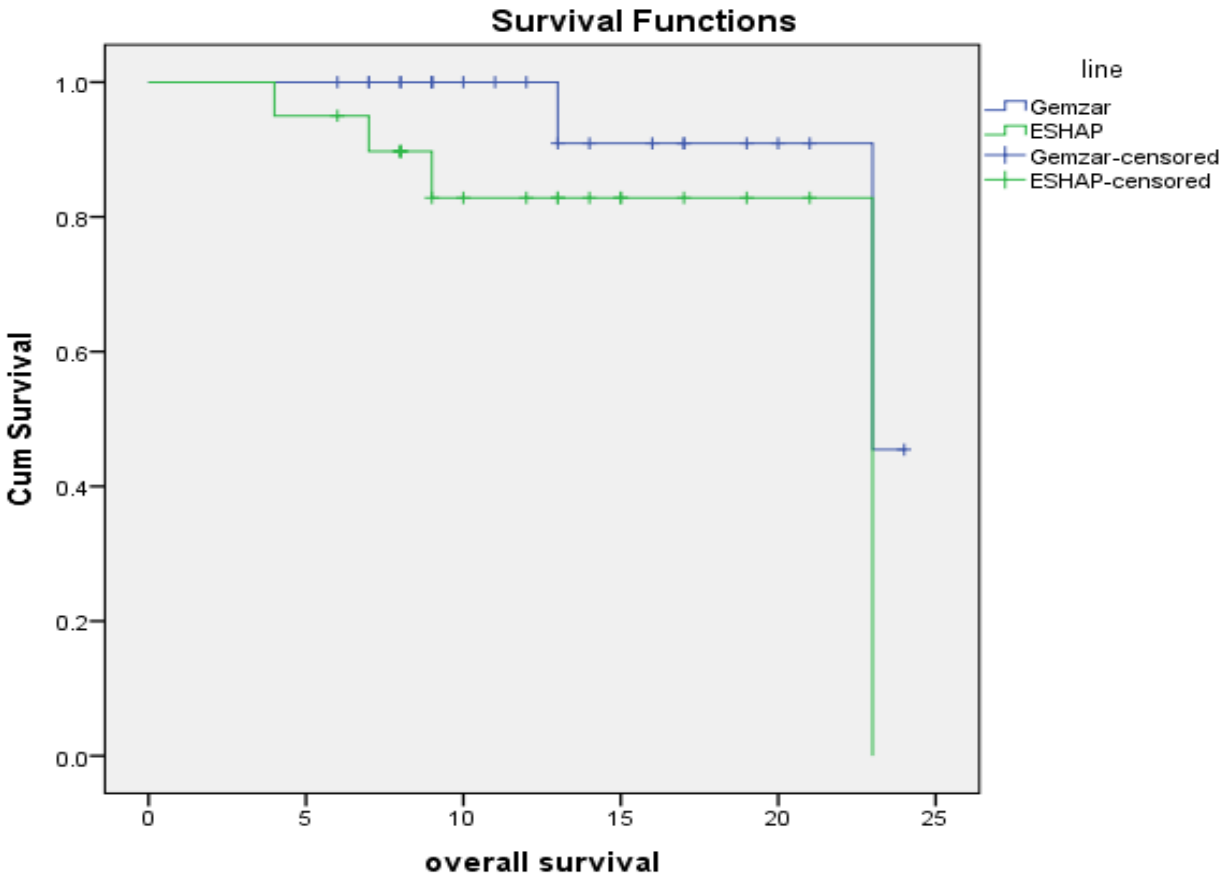
3. Results: Response rate

With amedian follow up period of 7 months (ranged 2-18 months), the response rate was (36.3%) in Gem/Carbo/dexa arm and (40%) in ESHAP arm with (P-value>0.05). complete remission was achieved in 3 patients (13.6%) and 2 (10%) in Gem/Carbo/dexa and ESHAP arms respectively. Partial remission was attained in 5 cases (22.7%) in Gem/Carbo/dexa arm and 6 (30%) in ESHAP arm respectively. Stationary course was in 3 (13.6%) cases in Gem/Carbo/dexa arm and 3 (15%) in ESHAP arm .but disease progression was 11 (50%) in Gem/Carbo/dexa arm and 9 (45%) in ESHAP arm.There was no statistically significant difference in response rate between the two arms (P-value=0.941).

Our results were inferior compared to the international figures because we couldn't give Rituximab in second line leading to poor response rate, on the

other hand, major percentage of patients didn't receive it in the first line due to financial causes leading to high percentage of primary refractory disease (gem carbo dexa 50%, ESHAP 40 %) leading to poor response rate and the fact that only about one third of patients had time to relapse more than 12 months(36.4% in gem carbo dexa arm and 30% in ESHAP arm). Also high percentage of patients 85% in ESHAP and 77..3% in Gem/Carbo/dexa arm has Stage (III – VI) adversely affecting the response rate.

The median time of overall survival probability in Gem/Carbo/dexa group was 23 months and in ESHAP group was 22.75 months with no statistical significant difference between both (P-value=0.174) and regarding time to disease progression, there was no statistically significant difference betweenthe two groups (12 months for Gem/Carbo/dexa vs. 18monthsforESHAP).



Toxicity

There were no statistical significant differences between both groups regarding treatment related hematological toxicity (P-value>0.05). the major hematologic toxicities of both armswereanemia,thrombocytopenia and neutropenia. And there were no statistical significant differences between both groups as regarding to the non hematologic toxicity as oral mucositis, GIT toxicity, Peripheral neuropathy and ototoxicity (P-value>0.05). but renal toxicity was increased in ESHAP arm as totoxicityit was reported in 5 cases related to 1 case only in Gem/Carbo/dexa arm.

Prognostic factors at relapse

factors affecting response rate were disease status at relapse (relapsed vs refractory),time to relapse after first line (less than or more than 12 months),IPI at relapse ,LDH and age adjusted IPI. (1)

4. Discusion:

Within the last two decades, the development and use of the monoclonal antibody (mAb) rituximab has dramatically improved the prognosis of NHL patients, and has been the standard of care in front-line treatment regimens however,The managementofrelapsed/refractory DLBCL represents a challenge for both the patients and the clinicians since more than half of these patients cannot be cured even with addition of rituximab. (4).

Autologus bone marrow transplantation is the standard of care in cases of chemotherapy- sensitive relapsed/refractory DLBCL and Hodgkin lymphoma . (6)

5. Conclusion:

We can say that gem carbo dexa regimen could be more convenient as this regimen is administered on 2 days on an outpatient basis, compared to 5 days inpatient in ESHAP arm. also gem carbo dexa regimen is less toxic than ESHAP regimen and may be considered in frail patients with renal impairment.

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