ORIGINAL ARTICLE

A Multicentre Phase-II Feasibility Study Evaluating Gemcitabine/ Vinorelbine / Prednisolone Combination Chemotherapy in Relapsed / Refractory Hodgkin's Lymphoma

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ABSTRACT

Objective: To determine the efficacy and toxicity of Gemcitabine, Vinorelbine and Prednisolone (GVP) salvage chemotherapy in relapsed / refractory Hodgkin's Lymphoma (HL).

Study Design: A phase-II non-randomized single arm study.

Place and Duration of Study: This study was conducted at Combined Military Hospital and Medical College Lahore, Mayo Hospital, King Edward Medical University, Lahore, Allied Hospital, Punjab Medical College, Faisalabad and Combined Military Hospital, Rawalpindi, from January 2007 to December 2007.

Methodology: Fifty adult patients with relapsed/refractory HL, adequate marrow reserve, hepatorenal and pulmonary functions, with radiological measurable disease and Karnofsky performance status of 0 – 2 non-candidates for stem cell transplantation, were enrolled. Four 28 days cycles of GVP (Gemcitabine 1000 mg/m^2, Vinorelbine 30 mg/m^2 on day 1 and 8 intravenously with oral Prednisolone 100 mg/day on day 1 – 5) were given. Response evaluation done according to Cotswolds meeting recommendations and toxicity was evaluated with NCI-CTC (National Cancer Institute - Common Terminology Criteria for adverse events v 3.0).

Results: Forty patients completing 4 cycles of GVP, 14 refractory/early relapse and 26 late relapsed (one year post-primary treatment with ABVD) were available for evaluation. The overall response (CRu+PR) rate was 77.5% with better response 85% in late relapsed patients. Haematological toxicity was most common and seen in 70% of cases.

Conclusion: GVP is well-tolerated regimen with high response rate and needs to be tested in late relapsed HL.

Key words: *Hodgkin's lymphoma. Salvage therapy. Relapse. GVP. Regime. Chemotherapy.*

INTRODUCTION

In about 20 – 30% of Hodgkin's Lymphoma (HL) patients, the disease either behaves refractory or relapses.[1] High dose therapy with Autologous Stem-Cell Transplantation (ASCT) is now considered a standard treatment in early relapse or refractory HL.[2,3] This treatment is not freely available especially in the developing world. Complete response (CR) to salvage therapy prior to ASCT is an indicator of improved long-term survival and in late relapses second durable CRs may be achieved in chemosensitive disease with salvage chemotherapy alone. A need for developing salvage therapy which is freely available, potentially curative and less toxic therefore, remains pertinent. Gemcitabine is a pyrimidine nucleoside antimetabolite that inhibits DNA synthesis and repair and has demonstrated activity in refractory HL.[4-6] Vinorelbine is a semi-synthetic vinca alkaloid, and its response rates as high as 50% have been reported including some CRs when given weekly as a single agent to patients with relapsed or refractory HL.[7-10]

Steroids are used in palliation and are documented to result in short lived partial responses and stable disease. Keeping in view the efficacy and mild toxicity profile of gemcitabine, a feasibility study of its combination with vinorelbine and prednisolone was planned in relapsed/ refractory HL. This pilot study was conducted to determine the tolerability and efficacy to this regimen in Hodgkin's Lymphoma before embarking on a large scale randomized trial comparing it with standard salvage regimens like DHAP.

The primary objective of this study was to determine the objective RR (CR+PR+CRu) and determination of safety of this regimen.

METHODOLOGY

This multicenter phase II study was conducted by Cancer Research Group Pakistan at Combined Military Hospital, Lahore, Mayo Hospital, Lahore and Allied Hospital, Faisalabad. The protocol was approved by the institutional review boards of all the involved institutions. Patients were enrolled after obtaining informed consent

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from 1st January to 31st December 2007. The study was performed in line with the Helsinki declaration, supported by a grant from Ministry of Health, Pakistan.

Entry criteria into study included adult patients with relapsed or refractory (non-responding) HL treated with ABVD chemotherapy, having adequate marrow reserve, normal hepatic, renal and pulmonary functions. These patients were not candidates for ASCT either due to comorbidities or non-availability and/or non-affordability. Eligibility criteria also included radiologically measurable disease and Karnofsky performance status of 0, 1, or 2. Pregnant and lactating females were excluded. Eligible patients who dropped before response assessment on completion of four cycles for any reason other than toxicity or tumour progression were also excluded.

This was a non-randomized, single-arm study. Each 28-day cycle of GVP included gemcitabine hydrochloride (Gemzar, Eli-Lilly, Italy) 1000 mg/m^2 on day 1 and 8 administered intravenously (i.v) over 30 minutes in 100 ml saline along with vinorelbine (Navelbine, ATCO) 30 mg/m^2 on day 1 and 8 by i.v bolus. Prednisolone was given orally 100 mg/day from day 1 – 5 of each cycle. Four cycles were administered on 28 days interval.

In case of myelotoxicity (ANC < 1.5 x 10^9/l and or platelet < 75 x 10^9/l) persisting until the next scheduled day of treatment, it was delayed until recovery. In case of a prolonged delay (> 7 days), due to neutropenia, or febrile neutropenia prophylactic filgastrim was mandatory for the following cycles starting day 9 for 7 days or and until absolute neutrophil count (ANC) exceeded 1,500 /µL. Twenty percent dose reduction in gemcitabine dosage was done in case of delay (> 7 days) due to persisting thrombocytopenia on day 8 or day 1 of next cycle. Twenty percent dose reduction for both vinorelbine and gemcitabine, if filgastrim was not effective in preventing neutropenia, or if there was febrile neutropenia. Day 8 therapy was withdrawn in case of ANC < 1.5 x 10^9/l and/or platelet < 75 x 10^9/l. Twenty percent dose reduction for both gemcitabine and vinorelbine was mandatory in case of grade-3 diarrhea, stomatitis, skin reactions, or grade-2 peripheral neuropathy. Treatment withdrawal was required if despite dose reduction there was persistent grade-3 or 4 skin reactions, grade > 3 peripheral neuropathy, grade-3 pneumonitis, grade-4 stomatitis, grade-4 thrombocytopenia, grade-4 neutropenia and/or febrile neutropenia, grade-4 anaphylactic reaction despite premeditation, progressive disease on interim evaluation after 2 months of treatment, intercurrent illness that prevented further administration of treatment, or if patient decided to withdraw from the study.

Response evaluation was done according to Cotswolds meeting recommendations.[11] Assessment was done after completion of two cycles and at the end of treatment. In patients not evaluated with fluorodeoxyglucose [^{18}F] positron emission tomography (FDG-PET) scanning for confirmation of complete remission (CR) status, complete remission unconfirmed (CRu) status was reported. It was defined by complete normalization of all disease related symptoms, relevant CT scanning documenting remission of lymphoid or visceral disease and normalization of any biochemical abnormalities assignable to HL. Partial response (PR) was defined as at least 50% reduction in the perpendicular diameter (PPD) of each area of measurable disease. Progressive disease (PD) was defined as at least 50% increase in the PPD of any involved site or new lesions. Stable disease (SD) was defined as less than PR, but without meeting criteria for PD. Patients were defined as responders to GVP if they achieved CRu and PR. Nonresponders included SD or PD.

Toxicity was evaluated according to the NCI-CTC (National Cancer Institute-Common Terminology Criteria for adverse events version 3.0). Toxicity evaluation was carried out before and on day 8 of each chemotherapy cycle and end of therapy. It was empirically decided to evaluate the feasibility of this regimen on a series of 50 consecutive patients. The regimen was estimated unfeasible if more than 6 patients prematurely discontinued from treatment because of toxicity.

Responses were calculated as percentages of all patients in the intent-to-treat population. Participants who received all four cycles of the regimen were included in the response and toxicity analysis.

Before performing the data-analysis, side effects typically associated to vinorelbine and gemcitabine was separately defined as drug specific and the overall incidence has been calculated by evaluating the number of patients who experienced the side effect at least one time during the treatment. Due to small and unequal sample size, only descriptive statistics were used.

RESULTS

Fifty patients of Hodgkin's lymphoma were recruited. Thirty patients were to be treated in the first stage. provided two or more confirmed responses (CR, CRu, PR) were noted in the initial cohort, 20 additional patients were to be entered into the second stage.

Forty patients were available for evaluation of response and treatment related toxicity/safety at final analysis. Patient characteristics are reported in Table I. The subjects included 26 late relapsed (one year post-primary treatment with ABVD) case and 14 refractory/early relapse case defined as progressive disease while on treatment or relapse within less than one year of ABVD treatment. All patients had a Karnofsky performance status of 0 – 2. The overall response rate (ORR) was 77.5%. In late relapsed patients response rate (RR) was 85% (95% CI; 0.56-0.99) with 16 CRu and

6 PR, 2 had stable disease and 2 progressed. In refractory/early relapsed: RR was 64% (95% CI; 0.48-0.89) with 6 CRu and 3 PR, one had stable disease and 4 progressed (Table II). Late relapsed patients showed a better response rate than early relapsed patients, 85 % vs. 64%.

Haematological toxicity was the most common and seen in 70% of cases (Table III). This was manageable with transfusions and use of growth factors. No serious bleeding diathesis occurred in cases developing grade-3 or 4 thrombocytopenia. Grade-1 and 2 vomiting, diarrhea, stomatitis, alopecia and peripheral sensory neuropathy were the other frequent adverse events.

Table I: Patient characteristics.

Characteristic	Number of patients
Total enrolled	50
Total evaluable (completing 4 cycles)	40 (80%)
Late relapses	26 (65%)
Primary refractory / early relapses	14 (35%)
Gender	
Male	28 (70%)
Female	12 (30%)
Age (years)	12 to 65
Anatomical sites for response evaluation	
Nodal disease	24 (60 %)
Mediastinal mass	4 (10 %)
Liver lesions	6 (15 %)

Table II: Response.

Outcome	Number of patients	
Total enrolled	50	
Assessable patients	40	
Response	Late relapsed 26 (65%)	Refractory/early relapse 14 (35%)
CR	16 (40%)	06 (15%)
PR	06 (15%)	03 (7.5%)
PD	02 (05%)	04 (10%)
SD	02 (05%)	01 (2.5%)
ORR (CRu, PR) = 77.5%	84.6%	64.2%

Table III: Adverse events (patients no = 40 evaluable).

Adverse event	Grade 1-2 Number of patients (%)	Grade 3-4 Number of patients (%)
Hypersensitivity reaction	Nil	Nil
Anemia	20 (50%)	6 (15%)
Leukopenia	18 (45%)	10 (25%)
Thrombocytopenia	20 (50%)	8 (20%)
Vomiting	22 (55%)	–
Diarrhea	8 (5%)	–
Stomatitis	28 (70%)	–
Alopecia	22 (55%)	–
Febrile neutropenia	–	6 (15%)
Sensory neuropathy	12 (30%)	–
Oedema	4 (10%)	–
Dyspnoea	4 (10%)	–
SGOT/SGPT rise	4 (10%)	–
Deranged renal function	2 (5%)	–

DISCUSSION

The optimum time and the right candidate to be considered for an autograft procedure remain undefined in many conditions. In HL disease, this procedure is recommended for all patients younger than 65 years who do not respond favourably to the first line chemotherapy. This treatment may still not be appropriate for patients with complete remission lasting more than 1 year, when the disease is possibly chemosensitive. In such settings and in the presence of comorbidities potentially increasing the risk of ASCT, a need for risk adopted strategy and considering a standard dose salvage therapy is logical.

Gemcitabine and vinorelbine (GV) combination is reported to be an effective and tolerable regimen in patients with metastatic breast cancer and advanced non-small cell lung cancer.[12,13] Its use in refractory lymphomas including Hodgkin's has also been tried and reported feasible in various studies.[14-18] Children's Oncology Group has recently reported ORR of 76% with this combination.[19]

It was shown that GV combination was highly effective in adult patients of relapsed/refractory HL when used in combination with Prednisolone (GVP) in the present study. The GVP regimen was well tolerable over four cycles of therapy, although dose modification were common. The RR was better (85%) in late relapsed patients compared to early relapse/refractory cases (64%). It is well realized that all the evaluated patients did not undergo a FDG-PET scanning due to unavailability thus CRs reported here are unconfirmed (CRu). However, considering the fact that negative FDG-PET are seen in residual masses regardless of size even earlier in the course of treatment, CT based response evaluation remains reliable and valid.

In terms of treatment related toxicity, this regimen was tolerable with dose modifications required in few cases for persisting myelosuppression. When side-effects are classified as gemcitabine specific like thrombo-cytopenia, the effect is not as pronounced as expected by adding another potentially myeloablative drug, vinorelbine. Febrile neutropenia was seen in 6 (15%) cases placing this regimen in intermediate risk for developing this toxicity and thus not requiring primary neutropenic prophylaxis.

CONCLUSION

GVP combination therapy is feasible in terms of response and toxicity and needs to be tested in a randomized trial against other salvage regimens in late relapse HL patients.

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