Non-platinum containing regimen of gemcitabine, vinorelbine and dexamethasone as salvage therapy in relapsed/ refractory Hodgkin's lymphoma

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Abstract

CONTEXT: Salvage regimens are used in relapsed/ refractory Hodgkin's lymphoma (HL) have variable efficacy and toxicity. The best responses are reported with combinations of gemcitabine, vinorelbine and liposomal doxorubicin but this has a high toxicity and additional cost of lipodox. We substituted doxorubicin with high-dose dexamethasone (GVDex) in the above regimen hoping to reduce toxicity and cost.

DESIGN: Retrospective data analysis. **PATIENTS OR OTHER PARTICIPANTS:** Data of patients of HL with relapsed/ refractory disease who received GVDex as second salvage (i.e after failure of either DHAP/ICE) or as first salvage (after first line ABVD/BEACOPP failure). The response rates, toxicity and transplant outcomes were captured from the records. All had pathologic documentation of HL at diagnosis and at relapse.

INTERVENTIONS: GVDexa was delivered as outpatient Q 3 weekly (G 1000 mg/m² IV D1, 8; V 25 mg/m² IV D1, 8; Dex 40 mg PO D1-4) for 2-3 cycles and then patients were evaluated and considered for auto-transplant if eligible. Patients received additional cycles in case delay was expected in transplantation or in non-transplant eligible patients.

MAIN OUTCOMES MEASURES: Overall response rate (ORR= CR+PR) and toxicity (CTCAE, version 4.0). **RESULTS:** Between 2010-2017, 49 patients received GVDex [median age 23 years (5-63); 33 (67%) males] of whom 27(55%) received it as first salvage (after failing ABVD/BEACOPP), and 22 (45%) received as second salvage (received DHAP/ICE after ABVD/BEACOPP). The median time from diagnosis to relapse was 18 months (4.2-127 months) and 23 (47%) patients had primary progressive disease. Advanced disease at relapse (Stage III/IV) was seen in 35(71%) patients. Median number of cycles: 3 (1-6). ORR (CR+PR) first salvage:70%(59+11); second salvage:50%(36+14). Toxicities: grade 3/4 neutropenia (N=15,30%), febrile neutropenia (N=8,16%), grade 2/3 ileus (N=2), grade 2 transaminitis (N=2), grade 2 hyperglycemia (N=2). Stem cell collection success rate after receiving only GVDex was 88%.

CONCLUSIONS: GVDex is a low-toxicity, cost-effective, highly effective out-patient salvage regimen with high response rate in relapsed/ refractory HL.

Background

- 70-80% of newly diagnosed patients with Hodgkin's lymphoma (HL) are cured with primary therapy.^{1,2}
 - 20-30% of them are either refractory or relapse after initial complete response and require salvage therapy.
- Standard treatment of relapsed HL involves salvage chemotherapy followed by high dose therapy (HDT) and autologous stem cell rescue (ASCT).
- Salvage therapy – multiple options exist
- Gemcitabine containing options are preferred
 - gemcitabine, vinorelbine and liposomal doxorubicin has reported responses 70%-80%
 - Toxicity high: 2/3 – febrile neutropeni
- GVDEX regimen:** replace liposomal doxorubicin with high dose dexamethasone

RESEARCH QUESTION

- What is the efficacy and toxicity of the GVDEX regimen in terms of response rates when used as salvage therapy in relapsed HL?

INCLUSION

- Relapsed/ refractory Hodgkin's Lymphoma
- Eastern Cooperative Oncology Group (ECOG) performance status of 0-2
- Repeat biopsy to confirm diagnosis
- Normal organ function

Features at relapse	N	%
Age, years		
Median	23	
Range	5-63	
Male sex	33	67
Stage at relapse		
II	14	29
III/IV	16	32
IV	19	39
Primary progressive disease	2	47
B symptoms	10	20
Prior therapy lines		
1	27	55
2 or more	22	45
Prior radiation	12	25
Prior salvage therapy (N=22)		
DHAP	18	
ICE	2	
DHAP and ICE	2	

REGIMEN delivered as Q21 day cycle

DAY	GEMCITABINE IV	VINORELBINE IV	DEXAMETHASONE Oral
D1	1000mg/m ²	25mg/m ²	40mg D1 to D4
D8	1000mg/m ²	25mg/m ²	X

DOSE MODIFICATIONS

- Treatment cycles were delayed till neutrophil count (ANC) was ≥1000/cmm or platelet counts ≥100,000/cmm prior to day 1 chemotherapy.
- The day 8 dose was not delivered if the ANC was <500/cmm and/ or the platelet count <50000/cmm. Blood counts were repeated after 2 days and the day 8 dose was administered with a 25% dose reduction once the ANC was ≥ 500/cmm and the platelets were ≥50,000/cmm.
- If the ANC didn't cross 500 by day 12 of the cycle, the day 8 chemotherapy was omitted in that particular cycle.
- Doses of vinorelbine and gemcitabine were reduced by 25% if any grade 3 non-haematological toxicities
- Grade 4 toxicity: further doses withheld**

Results

- Median time from diagnosis to GVDex: 18 months (4-127 months)
- Repeat biopsy confirmed HL: N=47 (96%)
- Median** number of cycles 3 (Range: 1-6)

TOXICITY

- Grade 3/4 neutropenia: N=15 (30%)
- Febrile neutropenia N=8 (16%)
- Grade 2/3 ileus: N=2
- Grade 2 transaminitis: N=2
- Grade 2 hyperglycemia: N=2

EVALUATION

- PET CT after 2-3 cycles
- CR: Deauville score 1-3 or resolution of LN
- PR: 50% reduction in size of LN with DS 4-5

END POINTS

- Overall response rate (CR+PR), toxicity
- Stem cell collection success rate
- Survival analysis by KM method
 - EFS: time from start of GVDex till progression or death due to any cause
 - OS: time from GV Dex till death

RESPONSES

Entire cohort

- CR: 24 (49%); PR: 6 (12)
- ORR: 61%

Responses with GVDex as first salvage

- CR: 59%; PR: 11%
- ORR: 70%
- The ORR among those with primary progressive disease (N=6) who received GVDex as first salvage was 67%

Responses with GVdex as second salvage of higher

- CR: 36%; PR: 14%
- ORR: 50%

STEM CELL TRANSPLANTATION

29/ 49 patients attempted stem cell collection

- Of these, successful collection was possible in 25 patients (86%)
 - 24 of these patients underwent autologous stem cell transplantation subsequently
- Among of the other 4 without collection, 3 received allogenic transplant
- Among those who received only GVDex as salvage and attempted stem cell collection (N=16) , all had successful collections

SURVIVAL

- After a median follow up of 16.1 months (2.5-57 months), the median OS of the entire cohort (from the start of GVDex) was 33 months (21-45) with a 2 year OS of 61%
- The median EFS was 14 months (5.2-22.6) and 2 yr EFS was 36%

Discussion

- GVDex is an easily deliverable, out-patient salvage regimen in relapsed HL for both adult and pediatric patients
- When used as first line salvage after failure of ABVD, the response rates are comparable to other regimens like GV+lipodox or IGEV which are more toxic
- A prospective trial is required to confirm these findings

References

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