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Research paper

Incidence and prognostic significance of nephrotoxicity in patients receiving eshap as salvage therapy for lymphoma

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ABSTRACT

Nephrotoxicity is a well-known side effect of platinum-based chemotherapy. We retrospectively assessed the incidence and prognostic impact of nephrotoxicity with ESHAP rescue chemotherapy in 74 lymphoma patients (61 aggressive lymphomas). A higher incidence of nephrotoxicity (estimated glomerular filtration rate < 60 mL/min) was found when ESHAP was administred on an outpatient vs. inpatient basis (14/39 vs. 4/35). Patients submitted to ASCT with renal failure had a lower overall survival (OS) than those with normal renal function (2-yr OS probability [95%CI]: 88% [77%–99%] vs. 50% [22%–78%]). Outpatient administration of ESHAP may not be optimal for all patients and the impact of ESHAP-induced renal failure on ASCT outcomes in lymphoma needs to be assessed in prospective studies.

1. Introduction

Platinum-based therapies are one of the most commonly used rescue strategies for patients with relapsed or refractory lymphoma before autologous stem cell transplantation (ASCT) [1–5]. The different platinum-based therapies, such as DHAP (dexamethasone, high-dose cytarabine and cisplatin), ESHAP (etoposide, methylprednisolone, high-dose cytarabine and cisplatin), GDP (gemcitabine, dexamethasone and cisplatin) and ICE (ifosfamide, carboplatin and etoposide) provide similar response rates [2–6].

Nephrotoxicity is a potentially severe side-effect of platinum compounds [7,8]. Prevention is mainly based on abundant hydration during treatment, but nephrotoxicity is not prevented in all cases. Its incidence ranges broadly between series and regimens but seems to be higher with 24-h infusion regimens (DHAP and ESHAP), being as high as 20% depending on the number of cycles and the definition of nephrotoxicity employed [4,5,7,8].

ESHAP with or without rituximab (ESHAP ± R) has been the salvage regimen used in our institution for the treatment of patients with relapsed or refractory lymphomas. Thus, we aimed to analyze the prevalence and prognostic impact of cisplatin-induced nephrotoxicity in these patients.

2. Patients and methods

Medical records from all adult patients with NHL or HL who received at least 1 of 3 intended cycles of ESHAP ± R as salvage therapy with the aim of subsequent ASCT consolidation between 2002 and 2014 were reviewed. Patients with renal failure (RF) (defined as an estimated glomerular filtration rate [GFR] < 60 mL/min according to the MDRD [modification of diet in renal disease] equation) before the start of ESHAP ± R were excluded from the study.

In our institution, patients considered able to follow an intensive p.o. hydration regimen and able to come to the clinic daily (i.e., living less than 30 Km away) received the regimen as outpatients by means of an i.v. pump and instructions to follow aggressive p.o. hydratation (> 4 L/day) alongside magnesium (4.25 mEq/day), calcium (500 mg/day) and bicarbonate (1 g/day) supplementation. Those who did not fulfill both conditions were admitted for in-hospital therapy (3 L/day of ½ normal saline with potassium, calcium and magnesium and 1 L/day of 1/6 M of sodium bicarbonate). For this study, patients were initially divided into two groups based on whether they received the treatment as inpatients or outpatients. Subsequently, patients who were able to undergo ASCT were divided into those with RF (defined as any degree of RF [GFR < 60 mL/min] persistent at the time of disease reassesment after ESHAP ± R) and those with normal renal function.

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ESHAP ± R consisted of etoposide 50 mg/m^2 and cisplatin 25 mg/m^2, in i.v continuous infusion (days 1 through 4), cytarabine 2 g/m^2, over 3 h (day 5) and methylprednisolone 250 mg iv (days 1 through 5) with rituximab 375 mg/m^2 on day 1 for B-cell lymphomas, repeated every 4 weeks for 3 cycles. Granulocyte-colony stimulating factor (G-CSF) was administered from day 6.

All patients received BEAM (carmustine 300 mg/m^2 on day −6, etoposide and cytarabine 100 mg/m^2 every 12 h on days −5 to −2 and melphalan 140 mg/m^2 on day −1) as conditioning regimen.

Association between baseline characteristics and study groups was studied by the chi-squared or Fisher's exact test, the Student's *t*-test or Kruskal-Wallis test, when appropriate. Survival curves were plotted according to the Kaplan-Meier method and were compared by the log-rank test. Follow-up was censored in December 2016. The Cox proportional hazards ratio model was used for univariate and multivariate survival analyses and relapse incidence and non-relapse mortality (NRM) were analyzed by competing risks analysis.

3. Results

Seventy-four patients fulfilled the inclusion criteria. Baseline features for the entire cohort as well as for the inpatient (n = 35) and outpatient (n = 39) groups are shown in Table 1. Outpatients were more likely to be male and more frequently presented with advanced stage at diagnosis. After ESHAP ± R, the response rate was similar, but outpatients were more likely to have RF (14/39 [36%] vs. 4/35 [11%], p = 0.017).

Of the 74 patients who received ESHAP ± R, 49 finally received ASCT, of whom 12 had RF (9 were treated in the outpatient group). The patients who proceeded to ASCT with RF were older (median age of 55 years vs. 35 years, p = 0.029) and less heavily pretreated (12/12 patients received 2 or less lines of therapy, vs. 26/37 [70%], p = 0.045) than patients with normal renal function. There were no differences in the status of the disease at the time of ASCT or the type of lymphoma. With a median followup of 6 years from the time of ASCT, patients who received ASCT with normal renal function showed a higher overall survival (OS) than those with RF (2-yr. OS from the time of ASCT [95% CI]: 88% [77%–99%] vs. 50% [22%–78%], p = 0.001, respectively) (Fig. 1). Although there were no statistically significant differences in relapse incidence or NRM (causes of death among patients with normal renal function included lymphoma progression [6 cases], infection [5 cases] and 1 stroke while patients with RF died of progression [2 cases], infection [3 cases], hemorrhage [3 cases] and myelodysplastic syndrome [1 case]), there was a trend towards an increased NRM in the RF group (2-yr NRM 3% [0%–12%] vs. 17% [2%–43%], p = 0.1).

Table 2
Response rates according to histological subtype.

	Inpatients			Outpatients		
	CR	PR	SD/PD	CR	PR	SD/PD
Hodgkin Lymphoma (n = 32)*	7	4	6	6	5	4
Diffuse large B-cell lymphoma (n = 22)*	3	2	4	8	4	1
Follicular lymphoma (n = 8)	2	2	–	1	2	1
Marginal zone lymphoma (n = 2)	–	1	1	1	–	–
T-cell lymphoma (n = 6)	1	1	–	3	1	–
Mantle cell lymphoma (n = 1)	–	–	–	1	–	–
Plasmablastic lymphoma (n = 1)	–	–	–	–	–	1
Small lymphocytic lymphoma (n = 1)	–	–	1	–	–	–

CR: Complete response; PR: Partial response; SD/PD: Stable disease/progressive disease.
* p value resulting from the comparison of CR/PR – SD/PD in outpatients vs. inpatients not significant.

4. Discussion

In this series of patients treated with ESHAP ± R followed by ASCT we found a decrease in OS in patients with cisplatin-induced RF, which was more likely to occur in those who received the treatment as outpatients than as inpatients.

An important finding of this study was that patients treated with ESHAP ± R as outpatients were more likely to develop RF. Despite the aparent good clinical tolerance to chemotherapy observed in these patients, the results of this study seem to indicate that patients could not follow an intensive enough p.o hydratation regimen when cisplatin was administered as a 24-h infusion.

The high rate of nephrotoxicity (24%) in the entire cohort is due to the stringent definition criteria employed. In most cases, RF was mild; grade 3 acute kidney injury according to the CTCAE version 4 requires an increase in serum creatinine above 3 times baseline levels, which was only seen in 1 patient in the present study, similar to what has been observed in most recent series [4,5,9] and notably lower than in earlier

Table 1
Baseline characteristics for the entire ESHAP ± R cohort and the patients that received the treatment as inpatients and outpatients.

		Whole series (n = 74)	Inpatients (n = 35)	Outpatients (n = 39)	p value
Male, n (%)		45/74 (61)	16/35 (46)	29/39 (74)	0.017
Age, median (range)		45 (20–70)	43 (20–70)	47 (22–69)	0.333
Lymphoma subtype, n (%)	HL	32/74 (43)	17/35 (49)	15/39 (39)	0.482
	NHL	42/74 (57)	18/35 (51)*	24/39 (62)**	
Ann-Arbor stage, n (%)	I-II	29/73 (40)	19/34 (56)	10/39 (26)	0.016
	III-IV	44/73 (60)	15/34 (44)	29/39 (74)	
Elevated LDH		17/30 (57)	5/10 (50)	12/20 (60)	0.705
IPI score*** (for NHL)	< 3	20/27 (74)	8/12 (67)	12/15 (80)	0.662
	≥3	7/27 (26)	4/12 (33)	3/15 (20)	
Refractoriness to chemotherapy before ESHAP	Response	59/74 (80)	30/35 (86)	29/39 (74)	0.225
	No response	15/74 (20)	5/35 (14)	10/39 (26)	
Abnormal eGFR before ASCT, n (%)		18/74 (24)	4/35 (11)	14/39 (36)	0.017
Response[a], n (%)	CR	33/74 (44)	13/35 (37)	20/39 (51)	0.266
	PR	22/74 (30)	10/35 (29)	12/39 (31)	
	SD/PD	19/74 (26)	12/35 (34)	7/39 (18)	

ESHAP ± R: Etoposide, methylprednisolone, cisplatin, high-dose cytarabine with/without rituximab; HL: Hodgkin lymphoma, NHL: non-Hodgkin lymphoma, LDH: Lactate serum dehydrogenase; eGFR: estimated Glomerular filtration rate, ASCT: Autologous stem cell transplantation, CR: Complete response, PR: Partial response, SD/PD: Stable disease/Progressive disease.
*Including 9 diffuse large B-cell lymphomas (DLBCL), 4 follicular lymphomas, T-cell lymphoma and marginal zone lymphoma (2 cases each) and 1 small lymphocytic lymphoma.
** Including 13 DLBCL (2 after histological transformation of a low-grade lymphoma), follicular lymphomas and T-cell lymphomas (4 each) and marginal zone lymphoma, plasmablastic lymphoma and mantle cell lymphoma (1 case each).
**Only applicable (where available) to DLBCL, follicular, marginal, plasmablastic and T-cell lymphoma.
[a] Table 2 shows response rates according to histological subtype.

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