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Paclitaxel, topotecan and rituximab: long term outcomes of an effective salvage programme for relapsed or refractory aggressive B-cell non-Hodgkin lymphoma

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Summary

Relapsed aggressive lymphomas are often treated with platinum-based chemotherapy (PBC) followed by an autologous stem cell transplant (ASCT). Response rates to PBC in patients with relapsed aggressive lymphomas are *c.* 60%, and non-responders have a dismal prognosis. Novel therapies for aggressive lymphomas, including those failing PBC, are needed. We performed a phase II study of paclitaxel, topotecan and rituximab (TTR) in patients with relapsed or refractory diffuse large B-cell, follicular grade IIIB, or transformed lymphomas, including those who previously failed PBC. The median age of the 72 patients enrolled was 54 years. Responding patients were offered ASCT after two courses. The overall response rate was 69% for all patients ($n = 49/71$) and 45% for those who previously failed PBC ($n = 9/20$). With a median follow up of 125 months for the censored observations, the overall survival (OS) and progression-free survival at 5 years was 39% and 27%, respectively. Responding patients who received ASCT had an OS of 63% at 5 years. Our results demonstrate that TTR is an effective salvage regimen for patients with relapsed aggressive B-cell lymphomas, including those who previously failed PBC. Given the

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Conflict of interest

We have no conflicts of interest related to the current manuscript to disclose.

declining therapeutic outcomes of salvage PBC in the rituximab era, further evaluation of TTR is warranted.

Keywords

non-Hodgkin lymphoma; chemotherapy; paclitaxel; topotecan; clinical trial

The management of patients with relapsed or refractory aggressive B-cell non-Hodgkin lymphoma (NHL) remains challenging (Friedberg, 2011). Up to 50% of patients with diffuse large B-cell lymphoma (DLBCL) will require a second-line therapy either due to primary regimen failure or relapse after achieving a complete remission. The most widely used second-line therapies for patients who are fit enough for an aggressive approach are platinum-based chemotherapy (PBC) regimens (Gisselbrecht *et al*, 2010). Ideally, patients who respond to a second-line PBC regimen are offered an autologous stem cell transplantation (ASCT) as consolidation (Philip *et al*, 1995).

Patients who do not respond to, or relapse after, second-line PBC regimens historically achieve very poor outcomes, and thus are frequently offered investigational, palliative or comfort care (Elstrom *et al*, 2010). In the pre-rituximab era, PBC regimens produced average response rates of between 60 and 80% (Philip *et al*, 1995; Martin *et al*, 2008; Gisselbrecht *et al*, 2010). The CORAL study randomized patients with relapsed CD20+ aggressive lymphoma to receive rituximab, ifosfamide, carboplatin and etoposide (R-ICE) or rituximab, dexamethasone, cytarabine and cisplatin (R-DHAP) (Gisselbrecht *et al*, 2010). There was no statistical difference in the overall response rate (ORR, 63% vs. 64%) and 3-year overall survival (OS, 47% vs. 51%) between R-ICE and R-DHAP, respectively. In the latest update of the CORAL trial, 43% of patients who progressed after PBC achieved a response to third-line therapy, though only 29% achieved a complete response (CR) and the median OS was 5.9 months (Van Den Neste *et al*, 2013). The development of more effective cytoreductive regimens with efficacy in platinum-refractory patients, which could potentially serve as an alternative to PBC regimens, will be required to improve outcomes for patients with relapsed DLBCL.

We have previously reported that the combination of paclitaxel and topotecan (TT) was effective salvage therapy for patients with relapsed or refractory aggressive B-cell NHL (Younes *et al*, 2001). In our previous trial, the ORR of TT was 48%, however only 12% achieved a CR. In patients who previously received PBC, the ORR of TT was 38%. Because the addition of rituximab to chemotherapy has improved response rates in patients with different types of B-cell NHL, we conducted a phase II study of paclitaxel and topotecan combined with rituximab (TTR) in patients with relapsed or refractory aggressive B-cell NHL. The goal of this study was to determine whether the addition of rituximab to paclitaxel plus topotecan would improve the efficacy in patients with relapsed or refractory aggressive B-cell NHL, including those who were refractory to PBC regimens.

Patients and methods

Patient eligibility

Patients with relapsed or refractory aggressive B-cell NHL were eligible if they were aged 18 years or older, had no more than two prior treatment regimens, a performance status of 2 on the Zubrod scale and at least one site of bidimensionally measurable disease. Laboratory requirements included an absolute neutrophil count $1.5 \times 10^9/l$, a platelet count $100 \times 10^9/l$, a bilirubin level 1.5 mg/dL, serum transaminase levels lower than twice the upper-normal values, and a serum creatinine level 1.8 mg/dL. Aggressive B-cell NHL was defined as the following histologies according to the World Health Organization (WHO) Lymphoma classification (Swerdlow *et al*, 2008): diffuse large B-cell lymphoma (DLBCL), follicular lymphoma grade IIIB (FL) and transformed B-cell lymphoma. Patients were excluded if they had human immunodeficiency virus infection, lymphoma involving the central nervous system, a history of serious cardiac disease, prior therapy with paclitaxel, topotecan or rituximab, prior treatment with high-dose chemotherapy and stem cell or bone marrow transplantation, or active infection. This was a single institution, single arm phase II study. Written informed consent was obtained from all patients in compliance with the Declaration of Helsinki, and the study was approved by the institutional review board.

Treatment plan

All patients received intravenous infusions of rituximab 375 mg/m² on day 1, paclitaxel 200 mg/m² on day 2, and Topotecan 1 mg/m² daily on days 2–6. Starting on day 7, patients received daily subcutaneous injections of granulocyte colony-stimulating factor (G-CSF) 5 µg/kg per day until neutrophil recovery. All patients were premedicated with intravenous infusions of dexamethasone 20 mg and diphenhydramine 50 mg, 30 min before paclitaxel infusion. Chemotherapy courses were repeated every 3 weeks in an outpatient setting. Patients who had disease progression after any course or did not achieve at least a partial response (PR) on restaging studies after two courses of TTR were removed from the study and offered alternative treatment, if possible. Patients who achieved a CR or PR after a minimum of two courses were offered ASCT. Patients who were not eligible for or refused ASCT were placed on observation after a maximum of six courses of TTR. Due to lack of experience with stem cell collection after the TTR regimen, it was preplanned to utilize ifosfomide, etoposide and rituximab as the mobilizing therapy combination. Thus, the study generated three distinct groups of patients: (i) responders who received autologous ASCT, (ii) responders who did not receive ASCT and (iii) non-responders.

Safety and response assessments

Patients were carefully monitored for toxicities during TTR infusions. Patients had a complete blood count (CBC) with differential twice weekly while on therapy and had a physical examination and chemistry profile before every course. Grading of adverse events was according to the Common Terminology Criteria for Adverse Events version 2.0 (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcmanual_v4_10-4-99.pdf).

Response to therapy was evaluated with imaging studies after every two courses and completion of therapy. Restaging studies included nuclear medicine scans (gallium and fluorodeoxyglucose positron emission tomography (PET/CT) scans) at the investigator's discretion, due to changing technology during the course of the trial. Long term follow-up observations included imaging studies every 3 months during the first year, every 4 months during the second year and every 6 months thereafter. If the pretreatment bone marrow biopsy revealed lymphomatous involvement, biopsies were repeated at the time of tumour assessment until clearance, and subsequently were performed only if clinically indicated at the investigator's discretion.

Statistical methods

The primary endpoint of the study was to determine the ORR (best response, CR + PR) of the TTR regimen. Secondary endpoints included evaluating the CR rate, safety and toxicities, progression-free survival (PFS) and OS. The study had two stratifications for patients with aggressive NHL: (i) primary refractory (defined as less than a CR to previous therapy) or (ii) relapsed (defined as achieved a CR to previous therapy with subsequent disease recurrence). It was anticipated that 40 patients in each subgroup would be enrolled for a total of 80 patients for the entire study. Based on our previous experience with paclitaxel and topotecan in a similar patient population, we anticipated a response rate of 25% in patients with primary refractory disease and 70% for patients with relapsed disease.

Survival, progression-free survival and response duration are defined according to the International Workshop to Standardize Response Criteria for NHL (Cheson *et al*, 1999) and were analysed using Kaplan–Meier survival estimates, with an α of 0.05 cutoff for statistical significance. Patients who received a pre-planned stem cell transplant as consolidation after response to TTR therapy were not censored for progression outcomes at the time of transplant. Patients who progressed after TTR and received a subsequent stem cell transplant were censored at the time of progression. All analysis were performed using SAS 9.1.3 (SAS, Cary, NC, USA), s-PLUS 8.0 (TIBCO Software Inc., Palo Alto, CA, USA), and PRISM 5 for MACINTOSH statistical software (GraphPad Software, Inc., San Diego, CA, USA).

Results

Patient characteristics

Seventy-two patients were enrolled on the study, beginning in November 1999, and all had completed the study therapy by January 2003. One patient withdrew consent before receiving therapy, leaving 71 patients who received at least one course of TTR and were evaluable for treatment response and toxicity. The trial began when rituximab was not commonly utilized in combination with chemotherapy, and thus no patients had received rituximab prior to TTR. The trial did not fully accrue the planned 80 patients due to the emergence of rituximab-based frontline therapies. The clinical characteristics of these evaluable patients are listed in Table I. The vast majority of patients had DLBCL ($n = 63$, 88%) and had received one prior therapy ($n = 63$, 88%). Of the nine with two prior regimens, seven were refractory to their most recent therapy, including six who were

refractory to PBC. Thirty-three patients (46%) did not achieve a CR to their first induction therapy (primary refractory). Of those who received prior PBC, 18 patients (90%) had failed to achieve a response (platinum refractory).

Efficacy

Seventy-one patients received a total of 282 courses of TTR therapy. Patients received a median of four courses (range 1–6 courses) and 22 patients were taken off study due to either disease progression during therapy or failure to achieve at least a PR after two courses of TTR. The ORR for all evaluable patients was 69% [95% confidence interval (CI), 57–79%], with 42% achieving CR (95% CI, 31–55, Table II). The response rate was higher in the group of patients with relapsed disease and those receiving only one prior therapy, though neither reached significance. Patients who initially relapsed <12 months after prior therapy or had received prior PBC had a lower response rate to TTR. Demographic factors including age at enrollment, number of extranodal sites and Ann Arbor stage were not significantly associated with response.

Survival

With a median follow up of 125 months for the censored observations, the median PFS for all patients was 18.4 months. The International Prognostic Index (IPI) score at study entry was the only significant factor for PFS and OS (Table III; Fig 1A, C). The median PFS for the group of patients who achieved CR or PR that was consolidated by ASCT was 70.6 months, with 3- and 5-year PFS rates of 56% and 52%, respectively (Fig 1B). The median PFS for the group of patients who achieved CR or PR and were observed without stem cell transplantation was 30 months, with 3- and 5-year PFS rates of 40% and 13%, respectively. The median PFS for the group of patients who failed to achieve at least PR was 2.2 months. Patients with primary refractory disease or early relapse had shorter median PFS and OS, though these did not reach statistical significance (Table III). The median PFS of patients who relapsed after a prior PBC was not statistically different from patients who were PBC-naïve (5 vs. 28 months, $P=0.25$) or OS (14 vs. 53 months, $P=0.32$) (Fig 2). Although the numbers are too small to draw any definitive conclusions, it should be noted that the two patients who were refractory to second-line PBC and responded to TTR remain alive with 10+ years of follow up.

The median OS for all patients was 38.7 months, was not reached in patients who achieved CR or PR and ASCT, and was 52.7 months in patients who achieved CR or PR but not ASCT (Fig 1D). The 3-year OS rates were 76% for the responsive/transplanted patients and 60% for the responsive/non-transplanted patients, respectively.

Safety

Treatment was well tolerated: Non-haematological toxicities were predominantly of grades 1 and 2. Seventeen percent of the patients experienced grade 3 or 4 fatigue, and 10% developed grade 3 sensory neuropathy. Grades 3 and 4 haematological toxicity were frequently observed; 56% of the patients developed grade 4 neutropenia (31% of the 241 treatment cycles) that lasted for an average of 3 d, and 39% developed grade 4 thrombocytopenia (25% of the treatment cycles). Grade 3 or 4 neutropenic fever was

observed in 30% of the patients and in 10% of the treatment cycles. All patients who attempted stem cell mobilization were able to collect an adequate number of cells.

Discussion

For patients with newly relapsed or refractory aggressive B-cell NHL who are eligible for high dose therapy, salvage PBC remains the standard of care. The two most common PBC regimens, ICE and DHAP were compared in the randomized CORAL study (Gisselbrecht *et al*, 2010). In the CORAL trial, the ORR was 63% and the 3-year OS was 50%, leading to the final conclusion was that there was no significant difference between the two tested regimens. The CORAL trial and others have shown that patients who fail to respond to PBC achieve very poor outcomes, with a median OS of <6 months (Elstrom *et al*, 2010; Van Den Neste *et al*, 2013). To improve outcomes for patients with relapsed or refractory aggressive B-cell NHL, novel salvage regimens with efficacy in platinum refractory patients are needed.

In this study, we treated 71 patients with relapsed and refractory aggressive B-cell NHL with the novel salvage regimen of paclitaxel, topotecan, and rituximab (TTR). This combination differs from commonly utilized salvage regimens in that it does not contain an alkylating agent, pyrimidine analogue, or a platinum compound. Despite these distinctions, TTR achieves high response rates and OS durations which compares favourably with existing PBC regimens. In addition, TTR does not require aggressive hydration and therefore can be easily given in the outpatient setting.

TTR produced an ORR of 69% and CR rate of 42%, which compares favourably to our previous experiences with paclitaxel and topotecan, alone and in combination (Table IV) (Preti *et al*, 1995; Arbutk *et al*, 1997; Younes *et al*, 1997, 2001; Kewalramani *et al*, 2004; Mey *et al*, 2006; Wiernik *et al*, 2012). The addition of rituximab in the current study also improved the ORR in patients with primary refractory or relapsed disease. Importantly, patients who responded to TTR and subsequently received consolidation with stem cell transplantation had a 3-year PFS of 56% (95% CI: 41–75) and OS of 76% (95% CI: 63–92). This compares favourably with data from the CORAL study where patients responding to PBC had 3 year PFS of 37% (Gisselbrecht *et al*, 2010). The 3-year PFS and OS for patients who responded but did not receive consolidation with stem cell transplantation, either due to patient refusal or ineligibility, was 40% (95% CI: 22–74) and 60% (95% CI: 40–91), respectively. These data also compare favourably to the PARMA trial, where the 3 year EFS and OS for non-transplanted chemoresponsive patients were *c.* 20% and *c.* 40%, respectively (Philip *et al*, 1995).

Although the ORR was lower in patients who received prior PBC, survival outcomes were similar after receiving stem cell transplantation (Tables II and III), implying that TTR may be an effective salvage regimen for patients with platinum-refractory disease. Our data show that TTR achieves outcomes similar with other widely used salvage regimens for relapsed aggressive B-cell NHL (Table IV). These data are encouraging, especially in light of reports that recommend palliative care for patients who failed prior salvage therapy (Ardeshtna *et al*, 2005; Elstrom *et al*, 2010).

We did not identify any significant difference in response or survival regarding the number of prior lines of therapy. This is especially interesting as most patients with two prior therapies were refractory to their most recent therapy and had received, and were refractory, to PBC. The number of patients refractory to second-line therapy in the current trial is small, but these data are in contrast to the observation by Seshadri *et al* (2008), who found that being refractory to second-line therapy was a strong predictor of additional salvage therapy failure.

It is important to note that this trial began when rituximab was not widely utilized in frontline therapy, and thus we excluded patients who received prior rituximab. It is unclear whether TTR will produce similar high responses in patients who have suffered disease progression after prior rituximab-based regimens. The addition to rituximab to the ICE salvage regimen was evaluated in patients with rituximab-naïve relapsed DLBCL (Kewalramani *et al*, 2004). Of the 36 eligible patients who were treated with R-ICE, 53% achieved CR and 25% achieved PR. The estimated 2-year PFS in patients who responded to R-ICE and subsequently received stem cell transplantation was 54%. This study had several differences in the eligibility criteria and design compared with our trial, including more homogeneous patients (only DLBCL), younger patients (median age was 45 years), and exclusion of patients who had more than one prior regimen or previously received platinum compounds. Despite these differences, both studies demonstrate the value of adding rituximab to salvage therapy in patients with DLBCL. However, it is important to note that both trials do not include patients who received prior rituximab, which is now included in standard front line induction regimens. In the CORAL study, patients who previously received rituximab had significantly worse outcomes with rituximab-based PBC when compared to rituximab-naïve patients (Gisselbrecht *et al*, 2010). Whether TTR can maintain high response and remission rates after rituximab-based primary therapy, and/or rituximab-based PBC is unknown. Answering this question would require further clinical trials of previously rituximab-exposed patients, as has been done for other salvage regimens. However, it is our opinion that based on the current data, it is reasonable to consider TTR therapy in fit patients who have failed prior rituximab-based primary therapy or rituximab-based PBC therapy.

This study did not examine the feasibility of stem cell collection using the TTR regimen due to lack of experience. For this reason, patients responding to TTR were given a cycle of rituximab plus ifosphamide and etoposide to mobilize stem cells prior to collection. However, other investigators have subsequently utilized taxane-based chemotherapy approaches for successful chemo-mobilization in patients with relapsed lymphomas (McKibbin *et al*, 2007; Sinha *et al*, 2011; Sinha *et al*, 2013).

In summary, our data demonstrate that TTR is a highly active, novel non-platinum-based salvage regimen for patients with relapsed and refractory aggressive B-cell lymphoma. The ability of TTR to induce remissions in patients who previously received PBC is encouraging and warrants further evaluation of this regimen in patients with relapsed aggressive lymphoma.

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Fig 1.

Survival data of TTR treated patients by group. (A) PFS based on IPI score at enrollment. (B) PFS in chemo-responsive patients who received ASCT (blue line), chemo-responsive patients who did not receive ASCT (orange line) and non-responders (red line). (C) OS by IPI score at enrollment. (D) OS for chemo-responsive patients who received ASCT (blue line), chemo-responsive patients who did not receive ASCT (orange line) and nonresponders (red line). TTR, paclitaxel, topotecan and rituximab; PFS, progression-free survival; OS, overall survival; IPI, International Prognostic Index; ASCT, autologous stem cell transplantation; CR, complete response; PR, partial response; E/N, number of events/number of patients.

Fig 2.

Survival data based upon prior platinum exposure. PFS (A) and OS (B) according to previous treatment with a platinum-based chemotherapy combination. PFS, progression-free survival; OS, overall survival; E/N, number of events/number of patients.

Table I

Enrollment clinical characteristics.

	<i>n</i> = 72	%
Age, years		
Median	54	
Range	(18–74)	
Sex		
Male	38	53
Female	34	47
Disease subtype		
DLBCL	63	88
FL grade III	5	7
Transformed	3	4
International Prognostic Index at relapse		
0	12	17
1–2	32	44
3–5	28	39
Extranodal site >1	25	35
Elevated lactate dehydrogenase	38	53
Number of prior regimens		
1	63	88
2	9	13
First therapy		
CHOP	56	78
Alternating triple therapy	14	19
Fludarabine	2	3
Second therapy	<i>n</i> = 9	
Platinum-based	6	67
Other non platinum	3	33
Exposure to platinum based prior therapy		
No	52	72
Yes	20	28
Refractory to first line therapy	33	46
Refractory to prior platinum-based therapy		
Yes	18	25
No	2	3
Time to relapse after diagnosis, months		
Median	10.8	
Range	(1.5–155)	

DLBCL, diffuse large B cell lymphoma; FL, follicular lymphoma; CHOP, cyclophosphamide; doxorubicin; vincristine; prednisone.

Response to TTR.

Table II

	<i>n</i> 71	Complete response	Partial response	ORR (CR + PR)	<i>P</i>
Response for all evaluable patients		30 (42%)	19 (27%)	49 (69%)	
Response according to number of prior therapies					
1	62	27 (44%)	17 (27%)	44 (71%)	0.44
2	9	3 (33%)	2 (22%)	5 (56%)	
Response according prior platinum-based regimen exposure					
Prior platinum	20	4 (20%)	5 (25%)	9 (45%)	0.006
No prior platinum	51	26 (51%)	14 (27%)	40 (78%)	
Response in patients refractory to second line PBC	6	0 (0%)	2 (33%)	2 (33%)	
Response according to response to initial therapy					
Refractory	32	9 (28%)	10 (31%)	19 (59%)	0.11
Responsive	39	21 (54%)	9 (23%)	30 (77%)	
Response according to time to relapse from initial therapy					
<12 months	40 *	13 (33%)	10 (25%)	23 (58%)	0.036
>12 months	30 *	16 (53%)	9 (30%)	25 (83%)	
Response according to enrollment LDH					
Elevated	37	11 (30%)	8 (22%)	19 (51%)	0.0009
Normal	34	19 (56%)	11 (32%)	30 (88%)	

ORR, overall response rate; CR, complete response; PR, partial response; PBC, platinum-based chemotherapy; LDH, lactate dehydrogenase.

* *N* = 70 for Response according to time to relapse from initial therapy, one patient had unknown values.

Table III

Survival data.

	Progression-free survival		Overall survival	
	Median (months)	At 5 years	Median (months)	At 5 years
IPI Score at study entry				
Low	42	45%	125	73% <i>P</i> < 0.0001
Low Intermediate	9	7%	34	14%
High Intermediate	9.5	28%	17	28%
High	3	0%	12	0%
Prior platinum				
Yes	5	25%	14	30% <i>P</i> = 0.32
No	28	27%	53	43%
Refractory to initial therapy				
Yes	6.5	26%	19	29% <i>P</i> = 0.13
No	28.8	28%	59	48%
Relapse from initial therapy				
<12 months	4.1	22%	19	31% <i>P</i> = 0.17
12 months	29.3	29%	59	49%

IPI, International Prognostic Index.

Table IV

Overall response rate for salvage therapy.

	N	Previous primary refractory (ORR %)	Previous relapsed (ORR %)	All patients (ORR %)	3-years PFS with ASCT	References
Paclitaxel	44	15%	50%	30%	NA	Younes <i>et al</i> (1997)
Topotecan	40	12%	43%	32%	NA	Preti <i>et al</i> (1995)
Paclitaxel + Topotecan	66	31%	65%	48%	NA	Younes <i>et al</i> (2001)
Paclitaxel + Topotecan + Rituximab	71	59%	77%	69%	56%	Current article
DHAP + Rituxan	53	23%	81%	62%	31%	Mey <i>et al</i> (2006); Gisselbrecht <i>et al</i> (2010)
ICE + Rituxan	36	46%	96%	78%	42%	Kewalramani <i>et al</i> (2004); Gisselbrecht <i>et al</i> (2010)

ORR, overall response rate; PFS, progression-free survival; ASCT, autologous SCT; DHAP, dexamethasone, cytarabine, cisplatin; ICE, ifosfamide, carboplatin, etoposide.