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Pixantrone is a Safe and Effective Therapeutic Option for Elderly Patients with Relapsed Refractory Diffuse Large B-Cell Lymphoma in the Real-World Setting

Verrou E*, Sevastoudi A, Karampatzakis N, Triantafyllou T, Dalampira D, Gogolopoulos S, Katsika L, Kamargianni M, Gkogkos DA, Laoutidis ER, Koutoukoglou P, Papadopoulou T and Katodritou E

Department of Hematology-Oncology, Theagenio Cancer Center, Greece

***Corresponding author:** Verrou E, Hematology Oncology Department, Theagenio Cancer Center, Al Symeonidi 2, 54639 Thessaloniki, Greece

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Abstract

Treatment of Relapsed/Refractory (R/R) Diffuse Large B-cell Lymphoma (DLBCL) remains an unmet need in every day clinical practice. Pixantrone is an approved by European Medicines Agency (EMA) for R/R DLBCL last generation anthracenedione developed to reduce the risk of cardiotoxicity. However real-world data regarding efficacy and safety of this agent are limited and controversial. In our study we analyzed 13 heavily pretreated elderly DLBCL patients who were treated with at least 1 cycle of pixantrone. The overall response rate was 46%; 3 patients achieved complete response and 3 patients had partial remission. All the responders were anthracycline sensitive as they had responded to anthracycline-based regimens upfront. Four responders had extranodal involvement (skin: 2, oropharynx: 1, oral cavity:1). Interestingly, 3 of the responders displayed long remission after first line therapy (87, 62 and 37 months, respectively). Regarding safety Pixantrone was well tolerated there was no treatment discontinuation due to Adverse Events. Our results indicate that Pixantrone is effective and safe in heavily pretreated DLBCL patients. Further studies are warranted to identify the subgroup of patients who may benefit from therapy with pixantrone and to identify the optimum positioning of the drug in the treatment of DLBCL.

Keywords: Diffuse large B cell lymphoma; Relapsed/refractory; Pixantrone

Abbreviations

DLBCL: Diffuse Large B- cell Lymphoma; R-CHOP: Rituximab-Cyclophosphamide Doxorubicin Vincristine Prednisone; R/R: Relapsed/Refractory; EMA: European Medicines Agency; ORR: Overall Response Rate; CR: Complete Response; PR: Partial Remission; SD: Stable Disease; PD: Progressive Disease; PFS: Progression Free Survival; OS: Overall Survival

Introduction

Diffuse large B-cell lymphoma (DLBCL) is the most common lymphoma sybtype, representing 30% of all lymphomas [1]. Although rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) is the standard treatment for patients with DLBCL, 30-40% of DLBCL patients eventually relapse and 10% are primary refractory, underscoring that, there is still an unmet clinical need regarding the treatment of DLBCL, especially in elderly or frail patients not eligible for hematopoietic stem cell transplant [2,3]. Recently, several innovative treatments for Relapsed-Refractory (R/R) DLBCL have been discovered including the anti-CD79b antibody drug conjugate Polatuzumab Vedotin, the oral nuclear transport inhibitor Selinexor and the bispecific antibody Tafasitamab in combination with Lenalidomide [4]. New drug development for R/R DLBCL over the past decade has overlooked cytotoxic chemotherapy drugs except for Pixantrone. Pixantrone is an approved by European Medicines Agency (EMA) last generation anthracenedione developed to reduce the risk of cardiotoxicity [5]. The molecular structure of pixantrone is close to that of mitoxantrone but without the 5, 8-dihydroxy substitution pattern. As a result, Pixantrone does not bind iron, therefore, it has less potential to generate reactive oxygen species and additionally is a relative weak inhibitor of Topoisomerase-II [6,7]. Pixantrone has been tested as a single agent in two prospective studies [8,9] but real-world data regarding efficacy and safety of this regimen in R/R DLBCL patients are limited. Herein we present a single-center experience of the use of Pixantrone outside the setting of clinical trials.

Materials and Methods

We retrospectively analyzed R/R DLBCL patients treated at our institution with Pixantrone as monotherapy between November 2017 and January 2022. All patients received Pixantrone at the recommended dose of 50 mg/m2 on days 1, 8 and 15 of a 28-day cycle, according to the prescribing information. Patients continued to receive treatment for up to 6 cycles, or until disease progression or death. Data regarding their lymphoma type, age, sex, stage, prior therapy lines, response and response duration were collected from the patients' records. We classified patients' histopathological samples according to the Hans algorithm into germinal center B-cell (GCB) and Activated B-cell (ABC) subtypes. Response rate was defined by the International Harmonization Project for Response criteria in lymphoma, that is Complete Response (CR), Partial Remission (PR), Stable Disease (SD), Progressive Disease (PD) and Overall Response Rate (ORR: CR plus PR rates). All procedures followed in this study were in accordance with the ethical standards of the Helsinki

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Declaration of 2000. Individual patient consent was not collected for this study as this was a retrospective database analysis however the standard institutional informed consent form for treatment signed by all patients, includes consent to use the patient's data, materials and/or test results for research purposes.

Results

Thirteen R/R DLBCL patients (female: 7, male: 6) were treated with Pixantrone for a median of 3 cycles (range 1-6). Median age of patients was 77 (range 67-87). Seven patients displayed GCB and six had ABC subtype of DLBCL. All patients were initially treated with R-CHOP or R-mini-CHOP. Regarding response assessment after first line treatment, 3/13 patients were considered as primary refractory. The median number of previous lines was 3 (range 2-5). Two patients were treated with Pixantrone in third line, 5 patients in 4th line, 4 patients in 5th line and 2 patients in 6th line. Ten patients had advanced stage (III/IV) of disease before Pixantrone administration and six patients displayed extranodal involvement. Finally nine patients had cardiovascular comorbidities before Pixantrone's administration.

Regarding efficacy of Pixantrone therapy ORR was 46%; 3 patients displayed CR after cycle 2, 4 and 6 respectively. Two of the patients who achieved CR were treated with Pixantrone as third line therapy and one as fifth line therapy. All patients who achieved CR were of GCB subtype; 2 of them had extranodal sites of involvement (skin and oropharynx respectively). Moreover, three patients showed PR; one after cycle 2 and two after cycle 4. According to pathology reports two of the patients achieving PR had ABC DLBCL subtype and one had GCB-DLBCL. Regarding extranodal disease two patients displaying PR demonstrated extranodal sites involving oral cavity and skin respectively. All six patients achieving either CR or PR had shown sensitivity to anthracyclines in the first line setting. Regarding duration of response to Pixantrone patients showing CR had a median duration of response of 11 months (range 2-17 months). Finally four patients had stable disease and three patients experienced progressive disease during treatment with Pixantrone. Median Progression Free Survival (PFS) after first line therapy among responders and non-responders to Pixantrone was 26.5 (range 13-82) and 11 months (range 0-25) accordingly. Characteristics of patients are summarized in (Table 1).

Regarding safety 3 patients developed in total 4 episodes of neutropenia grade 3, one patient developed two episodes of grade 3 thrombocytopenia and one patient experienced 2 episodes of grade 3 anemia requiring red blood cell transfusions. No neutropenic fever was recorded during Pixantrone treatment. Cardiac toxicity was also not evident, and no patient discontinued therapy due to Serious Adverse Event.

Discussion

Treatment with R-CHOP has improved substantially survival rates of patients with DLBCL however treatment of R/R DLBCL remains a challenge especially for older patients, considering that they display unfavorable biological features, geriatric vulnerabilities and cumulative toxicities of the previously applied chemotherapy, which may compromise therapeutic efficacy. Approval for the use of Pixantrone monotherapy was issued by EMA in 2012 for patients with R/R DLBCL in the 3rd or 4th line setting who had previously received a rituximab-containing immunochemotherapy. However, its use was overwhelmed, after the development of more effective agents such as Polatuzumab Vedotin or Chimeric Antigen Receptor-T cell therapies. Although not widely used Pixantrone has showed occasionally impressive results as a bridge for autologous transplantation [10] or even in R/R patients after allogenic transplantation [11]. More recently a few studies evaluated safety and efficacy of Pixantrone in combination with other agents [12]. Nevertheless, in the era of molecularly targeted therapies Pixantrone appears like an old-fashioned cytotoxic drug that tries to find its position in the landscape of salvage therapy of RR DLBCL.

Approval of Pixantrone by EMA was based on the results of an international, multicenter, randomized, active-controlled, open-label Phase III study (PIX301) [9]. According to the results of PIX301 CR or unconfirmed CR (uCR) and ORR were significantly higher with Pixantrone monotherapy compared with physician's choice chemotherapy regimens: 20% vs 5.7% ($p = 0.021$) and 37.1% vs 14.3% ($p = 0.003$), respectively. Moreover, PFS was significantly longer in the Pixantrone group; in addition, Pixantrone was generally well tolerated, with a manageable safety profile. Interestingly a recently published extended survival analysis reported that some of the patients achieving a CR or uCR at the end of the PIX301 trial, survived >400 days without progression [13].

Although the results of PIX301 seemed encouraging, data from real-world studies appear controversial. Two observational studies [14,15] displayed efficacy of Pixantrone in R/R DLBCL in the real-world setting, whereas other studies demonstrated only limited efficacy [16,17]. Zinzani et al reported fifteen heavily pretreated DLBCL patients treated with Pixantrone with an ORR of 26.7% and with a best response rate of 46.7% [14]. Moreover Sancho et al also reported encouraging results of 79 patients treated with Pixantrone showing an ORR of 29% with 13.2 % and 15.2% of the patients achieving CR and PR accordingly. Median PFS after Pixantrone therapy was 2.8 months (95% Confidence Interval [CI] 2.1-3.6) and median Overall Survival (OS) was 4.0 months (95% CI 5.6-7.9). Interestingly patients receiving ≥2 cycles of Pixantrone showed improved results comparing to the overall patients population [15].

Table 1: Patient Characteristics and Response.

Sex/Age	Number of previous lines	PFS of 1th line	Stage at Pixantrone	Extranodal sites	ABC /GCB	Response
M87	2	62	IIAE	Skin	GCB	CR
F68	4	15	IA	-	GCB	CR
F81	2	37	IVA	Oropharynx	GCB	CR
F77	3	82	IIIA	-	ABC	PR
F67	4	13	IVA	Skin	ABC	PR
F78	5	16	IVA	Oral cavity	GCB	PR
M80	4	12	IVA	Lung	GCB	SD
M75	3	18	IVA	Bone	ABC	SD
M76	4	11	IIIB	-	GCB	SD
M74	5	2	IIIA	-	ABC	PD
F70	3	0	IIIB	-	ABC	PD
M83	3	25	IIA	-	GCB	PD
F82	3	2	IIIA	-	ABC	SD

Table 2: Patient characteristics and outcomes, a comparison between the PIX301 study, UK retrospective analysis, the study of Novacovic et al and the present study.

Variable	Pixantrone arm Phase III trial	UK analysis	Novacovic et al	Present study
Number	70	90	12	13
Median age	60	66	65	77
Males%	66	66	25	46
Stage III/IV,%	73	90	100	77
Sensitive to anthracyclines,%	100	71	25	77
Duration of first response< 12 months,%	0	40	92	23
Overall Response Rate	CR=20% , PR=17%, ORR=37%	CR/Cru =10%, PR=14%, ORR=24%	ORR=0%	CR=23%, PR=23%, ORR=46%

In contrast to the previous studies, a UK-wide retrospective multicenter study of 92 R/R DLBCL who received Pixantrone showed an ORR of 24% (CR: 10%; PR: 14%). The median PFS was 2 months with a 95% Confidence Interval (CI) 1.5–2.4 months; the median OS was 3.4 months (95% CI 2.7–4.5) [16]. In the multivariate Cox regression patients who relapsed >12 months after first line treatment, those with fewer prior lines of therapy and relapsed (non-refractory) DLBCL had better PFS.

Similar results were reported by Novakovic et al in a small study including 12 patients. All patients progressed during treatment and none of the patients was alive at the time of analysis due to progressive lymphoma. Pixantrone specific median OS was 3.5 months (range, 0.5-10 months). Interestingly, a marginally superior median OS (p=0.065) was observed in patients primarily sensitive to anthracyclines [17].

In our study, we observed a comparable CR rate (23%) with the one reported in the PIX301 trial [9] as shown inTable 2. We also confirmed the observations of the retrospective Spanish and Italian real-world studies [14,15] suggesting that Pixantrone could be an effective and reasonable option for R/R DLBCL patients in the real-world setting. In contrast, our results are not in accordance with the observations of the large UK retrospective study and the smaller study of Novakovic et al showing limited efficacy of Pixantrone in RR DLBCL patients [16,17]. The controversies of the results among various real–world studies assessing potency of Pixantrone in DLBCL patients could be explained by the different characteristics of the patients included in these studies. For example in the study of Novakovic et al 58% of the patients had primary refractory disease (Table 2). At variance, our study population included only 3 (23%) patients primary refractory to R-CHOP. It is also noteworthy that 4 out of 6 patients showing response to Pixantrone in our study had extranodal disease involving skin, oropharynx and oral cavity. Remarkably one patient with extranodal involvement achieving CR, experienced a long-term remission of 17 months and finally died due to stroke. Although our study had a limited number of patients the latter observation of the possible efficacy of Pixantrone in extranodal involvement should be examined in larger studies. Finally, three of our patients achieving CR or PR with Pixantrone had a prolonged PFS after R-CHOP indicating that Pixantrone could be effective in chemosensitive patients and confirming the results of previous studies revealing superior outcomes in patients who relapsed >12 months after first line treatment [16]. Additionally, all the responders were sensitive to anthtracyclines and 2 of them received Pixantrone as a third line confirming that patients with fewer prior lines of therapy who were not primary refractory to R-CHOP may be more sensitive to Pixantrone. Interestingly our study indicating these satisfactory results included more elderly patients in comparison with previous studies as shown in (Table 2). Regarding safety, Pixantrone was well tolerated, despite the advanced median age of treated patients. No patient discontinued treatment due to adverse events and no cardiac toxicity was noted among our population. Generally, the safety profile in our elderly population was consistent with what was expected based on previous studies [12].

In a recently published study, Tarantelli et al, demonstrated a high efficacy of Pixantrone in combination with targeted therapies in lymphomas, suggesting an add-on value of this drug, in the novel agent era [18]. Moreover, Muszbek et al assessing the health economic implications of Pixantrone versus Current Clinical Practice (CCP) in the United Kingdom for R/R Non Hodgkin Lymphoma patients concluded that Pixantrone may be not only a safe but also a cost-effective option for patients with R/R DLBCL [19].

In conclusion, our results indicate that Pixantrone may be an effective therapeutic option for elderly R/R DLBCL patients, who displayed sensitivity to anthracyclines in the first line setting especially if they are experiencing late relapse. Considering that the algorithm of R/R DLBCL has yet to be established, we believe that Pixantrone could be used alone or in combinations with other agents in chemosensitive relapses [18], even as a bridge to novel therapies. Further large real-world studies are warranted to identify the clinical and biological features of patients who may benefit from therapy with Pixantrone and to delineate the position of this agent in the salvage setting of DLBCL.

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