Review article

Pixantrone – anticancer drug in the monotherapy of aggressive lymphomas

Janusz Hałka

Clinical Department of Hematology,

Warmian-Masurian Cancer Center of The Ministry of The Interior and Administration's Hospital, Olsztyn, Poland

ABSTRACT

Pixantrone is a first drug aza-anthracenedione approved as monotherapy of relapsed or refractory aggressive lymphomas. This drug has the unique chemical structure and mode of action properties distinguishing it from anthracyclines and anthracenediones. Pixantrone is one of the treatment option for heavily pretreated patients which to receive their living with doxorubicin and the further application from anthracyclines potentially can lead anthracycline-induced congestive heart failure.

The benefit of pixantrone treatment has not been established in patients when used as V line or greater chemotherapy in patients who are refractory to last therapy. In general, pixantrone seems to be safe and manageable. In various trials, there were no unexpected side effects reported and no trials were closed prematurely because of side effects. In an evaluation of 12 clinical trials with pixantrone, the most common side effect (all grades) was hematological toxicity, mainly neutropenia (50% of patients; grade third/fourth: 41%), leukopenia (25%), anemia (31%), and thrombocytopenia (21%). Hematological toxicity was the main reason for a delayed start of subsequent cycles or for omitting the day-15 dose of pixantrone. In the outpatient setting, it is worth considering the use of hematopoietic growth factors. Other side effects included asthenia (23%), pyrexia (23%), and nausea, most patients experienced reversible skin discoloration.

Key words: pixantrone, aggressive non-Hodgkin lymphoma, cardiotoxicity

Correspondence:
Janusz Hałka
Clinical Department of Hematology, Warmian-Masurian Cancer Center of The Ministry of The Interior and Administration's Hospital

Received:
15.06.2020
Accepted:
30.06.2020

DOI: 10.24292/01.OR.220300620.2

Non-Hodgkin lymphoma (NHL) comprises a heterogeneous group of lymphoproliferative disorders. It is the fifth most common cancer in the Unites States and Europe, with an increasing incidence over the past four decades. Diffuse large B-cell lymphoma (DLBCL) is the most common NHL subtype and accounts for 75% of all aggressive lymphomas. The crude incidence in the western world is about 3.8/100,000/year. Anthracycline-based chemotherapy regimens are often used in hematological malignancies they are most effective in NHL. Anthracycline-containing multidrug regimens are the current standard of care for I line treatment of NHL for example DLBCL [1, 3, 5, 6, 9, 10]. In patients who relapse or who have disease refractory to I line therapy treatment options are limited. Anthracyclines may be effective in II line therapy but their use is limited by cumulative cardiotoxicity as a result of irreversible damage to myocardial tissue .The development of anthracyclines started in the 1950's with the discovery of doxorubicin and daunorubicin followed by the development of the anthracenedione – mitoxantrone in the 1970's. These compounds showed a high activity against all types of NHL. Anthracyclines block the function of topoisomerase II (TOP2) with its isoforms α and β, an enzyme that effects tension and topologic features of DNA, which results in disrupting the tumor growth. However, it was quickly learned that anthracyclines also exhibit significant cardiotoxicity, presumably by driving reactions that result in the formation of free radicals and the generation of reactive oxygen species (ROS), which in turn can react with and disrupt the function of cells A serious side effect of long-term doxorubicin is cardiomyopathy followed by congestive heart failure (CHF). Delayed cardiomyopathy can occur with cardiac damage becoming evident 4–20 years after completing treatment [5, 10]. Previous studies have shown that the total anthracycline cumulative dose is an important risk factor for the development of anthracycline-induced CHF. The incidence of cardiac events and CHF is associated with the cumulative doxorubicin dose with clinical CHF occurring in approximately 25% of patients who have received > 500 mg/m^2 doxorubicin. After I line therapy for NHL, most patients have already received their lifetime limit of doxorubicin, approximately 400 mg/m^2, and therefore there exists the need for an alternative effective yet less cardiotoxic treatment. The anthracycline derivative mitoxantrone, an anthracenedione, has a better toxicity profile compared with doxorubicin but is also associated with cardiac toxicity [1, 5, 10].

Pixantrone is a novel aza-anthracenedione anthracycline derivative manufactured by Cell Therapeutics Incorporated. Pixantrone is an alternative II line therapy in refractory or relapse non-Hodgkin lymphoma. The drug has been approved by EMA on May 10th, 2012 (no. EU/1/12/764/001) and in 2009 by CTI applied to the US FDA for accelerated approval of pixantrone in patients with relapsed or refractory NHL.

Pixantrone – pixantrone dimaleate (6,9-bis[(2-aminoethyl)amino]benzo[g]isoquinoline-5,10-dione) is an aza-anthracenedione and DNA intercalator which inhibits topoisomerase II. Pixantrone is similar structure to anthracyclines such mitoxantrone, but exerts fewer effects on cardiac tissue. Moreover, in contrast with antracyklines and antracenediones pixantrone directly a DNA is alkylating creating long-lasting additive connections with the DNA and leading double thread to the interrupt. Moreover, because of building the heteroatom of nitrogen in to the ring and the lack of ketonic groups pixantrone has a lower potential of producing reactive oxygens binding iron and creating metabolites of alcohol which is regarded responsible for cardiotoxic action anthracyclines. Due to one's unique structure, in animal models pixantrone exerted the minimum cardiotoxic income in the comparison from doxorubicin and mitoxantrone. The cytotoxicity of pixantrone does not directly correlate with the DNA damage induced by DNA cleavage via topoisomerase II alone. Formaldehyde can activate pixantrone extrinsically to form covalent drug – DNA adducts. Formaldehyde-activated pixantrone alkylates DNA selectively at CpG and CpA dinucleotides via the terminal primary amino group of a single drug side chain. CpG islands are associated with regulatory promoter regions of many mammalian genes and aberrations in CpG methylation patterns are a known feature of most cancers. Cancer-specific methylation of CpG islands is a feature of several tumor suppressor genes, DNA repair genes and genes suppressing angiogenesis, invasion and metastasis. Cancer cell line studies have shown that CpG methylation potentiates pixantrone-induced DNA damage and is therefore a marker of drug sensitivity. Metabolism does not appear to be an important route of elimination for pixantrone. Rather, biliary excretion of unchanged pixantrone may be the primary route of elimination. Data suggest a high hepatic extraction ratio for pixantrone, with hepatic uptake possibly mediated by the transporter OCT-1 and biliary excretion possibly mediated by the transporters P-gp and BCRP. Plasma clearance of pixantrone was 72.7 l/h with renal excretion accounting for 10% of the dose in the 24 h following administration. Pixantrone had a mean terminal elimination half-life ranging from 14.5 to 44.8 h, with mean and median values of 23.3 and 21.2 h [1, 4–6, 8–10]. No formal drug-drug interaction studies have been conducted, no interactions between pixantrone and other agents (e.g. cytarabine, cisplatin, methylprednisolone) were reported in clinical studies. Theoretically, co administration of pixantrone may increase plasma concentrations of CYP1A2 substrates (e.g. theophylline, warfarin, amitriptyline, haloperidol, clozapine, ondansetron, pro-

pranolol). Pixantrone was a substrate for the transporters P-gp, BCRP and OCT-1; inhibitors of these transporters (e.g. ciclosporin, tacrolimus, ritonavir, saquinavir, nelfinavir) have the potential to decrease the elimination of pixantrone. In addition, caution is recommended when pixantrone is continuously co administered with inducers of efflux transporters (e.g. rifampicin, carbamazepine, glucocorticoids), as the systemic exposure of pixantrone may be decreased. Patients received intravenous pixantrone 50 mg/m^2 on days 1st, 8th and 15th of a 28-day cycle for up to six cycles [5, 10].

The drug registration trial was The EXTEND (PIX301). The EXTEND trial was a randomized, multicenter, controlled, open-label phase III study looking at patients with aggressive NHL with at least two prior anthracycline-containing regimens [1–3, 5, 6]. Patients were randomized to pixantrone 85 mg/m^2 on days 1st, 8th and 15th every 28 days for up to six cycles, or to an alternative single-agent comparator of the investigator's choice: vinorelbine, oxaliplatin, ifosfamide, etoposide, mitoxantrone or, in the USA only, gemcitabine or rituximab [7]. Both groups of patients were followed-up for 18 months from the date of their last treatment. Due to slow accrual, a total of 140 (out of the 320 planned) patients were randomized in the study. The median number of cycles in the pixantrone group was four compared with three in the comparator group. At the end of the study, the CR/CRu rate was 24% in the pixantrone group with an ORR of 40% compared with a CR/CRu rate of 7% with an ORR of 14% in the comparator group. After treatment, three patients in the pixantrone group achieved CR without further therapy, two of the patients went from stable disease (SD) to CR and one of them went from PR to CRu. Median CR/CRu duration was 9.6 months in the pixantrone group compared with 4 months in the comparator group. The median PFS in the pixantrone groups was 5.3 months with median OS of 10.2 months compared with a PFS of 2.6 months and OS of 7.6 months in the comparator group. As expected, neutropenia and leukopenia were the most common CTC grade third/fourth toxicities with a 7.4% incidence of febrile neutropenia in the pixantrone group and 3% in the comparator group. Thirteen patients in the pixantrone group compared with seven in the comparator group had asymptomatic decreased LVEF (> 10% decrease). This is difficult to interpret as patients in the pixantrone arm had a significant cardiac history at entry (three patients in the pixantrone group had a history of CHF and two had ongoing cardiomyopathy compared with no patients with either condition in the comparator group) compared with the control arms. All but one of the LVEF declines during treatment were CTC grade first or second. There was no correlation between cumulative anthracycline exposure and CHF incidence. This phase III study showed that pixantrone achieved a superior efficacy measured by the CR/CRu rate and by the ORR and PFS with a positive trend in OS. The Food and Drug Administration (FDA) is considering approval of pixantrone in the case of relapsed or refractory aggressive NHL based on these data. The currently recruiting randomized multicenter phase III study (PIX-R) comparing pixantrone plus rituximab with gemcitabine plus rituximab in patients with DLBCL who have relapsed after prior therapy with CHOP-R or an equivalent regimen and are ineligible for stem cell transplant should clarify the results of the EXTEND (PIX301) trial.

The EXTEND (PIX301) trial demonstrated that pixantrone had a superior CR/CRu, ORR and PFS compared with other single-agent chemotherapy drugs (tab. 1) with a tolerable safety profile (toxicities associated with pixantrone include nausea, vomiting, lymphopenia, thrombocytopenia, blue discoloration of the skin and urine as well as alopecia) [6, 9]. Overall pixantrone appears to be a well-tolerated drug with manageable side effects. In general, pixantrone seems to be safe and manageable. In various trials, there were no unexpected side effects reported and no trials were closed prematurely because of side effects. In an evaluation of 12 clinical trials with pixantrone, the most common side effect (all grades) was hematological toxicity, mainly neutropenia (50% of patients; grade third/fourth: 41%), leukopenia (25%), anemia (31%), and thrombocytopenia (21%). Hematological toxicity was the main reason for a delayed start of subsequent cycles or for omitting the day-15 dose of pixantrone. In the outpatient setting, it is worth considering the use of hematopoietic growth factors. Other side effects included asthenia (23%), pyrexia (23%), and nausea. Most patients experienced reversible skin discoloration [5, 6, 8, 9].

Patients with relapsed non-Hodgkin lymphoma typically receive intensive regimens such as R-ICE (rituximab, ifosfamide, carboplatin, and etoposide) or R-DHAP (rituximab, dexamethasone, cytarabine, and cisplatin), with stem-cell transplantation for those who respond to chemotherapy. The use of pixantrone as an anthracycline with reduced cardiotoxicity in salvage therapy of aggressive NHL, particularly in patients relapsing post rituximab treatment, would add a very effective drug to existing therapeutic options. In the future it will be important to assess efficacy and safety earlier in therapy and in combination with other cytotoxic agents to reduce the burden of both early and late cardiac morbidity and mortality in patients being treated with curative intent. If randomized clinical trials confirm the efficacy of pixantrone in combination regimens, it can be used in earlier lines of therapy, which would be ideal in frail elderly patients and in those with known cardiac co-morbidities.

Tabela 1. Efficacy of pixantrone monotherapy in patients with relapsed or refractory aggressive non-Hodgkin lymphoma: results of the PIX301 trial (based on [6]).

	Pixantrone	Comparator	Hazard ratio (95% CI)
Response rates at end of treatment (% of patients)			
	CR/uCR rate	20.0*c	5.7c
	CR rate	11.4**	0
	uCR rate	8.6	5.7
	ORR	37.1**	14.3
Response rates at end of study (% of patients)			
	CR/uCR rate	24.3**	7.1
	CR rate	15.7***	0
	uCR rate	8.6	7.1
	ORR	40.0***	14.3
Other endpoints			
Median duration of CR/uCR (months)	9.6	4.0	0.32 (0.09–1.23)
Median PFS (months)	5.3**	52.6	0.60 (0.42–0.86)
Median OS (months)	10.2	7.6	0.79 (0.53–1.18)

CR – complete response; ITT – intent-to-treat; IV intravenous; ORR – overall response rate; OS – overall survival; PFS – progression-free survival; uCR – unconfirmed CR.
* p\0.05, ** p\0.01, *** p B 0.001 vs. comparator agent.
[a] 68 patients received IV pixantrone 85 mg/m^2 on days 1st, 8th and 15th of a 28-day cycle.
[b] the ITT population comprised 70 randomized patients b 67 patients received a comparator agent [IV vinorelbine 30 mg/m^2 on days 1st, 8th and 15th and 22nd of a 4-week cycle (n = 11), IV oxaliplatin 100 mg/m^2 on day 1st of a 3-week cycle (n = 30), IV ifosfamide 3000 mg/m^2 on days 1st and 2nd of a 4-week cycle (n = 12), IV etoposide 100 mg/m^2 on days 1st, 2nd, 3rd, 4th and 5- of a 4-week cycle (n = 4), oral etoposide 50 mg/m^2 once daily for 21 days of a 4-week cycle (n = 5), IV mitoxantrone 14 mg/m^2 on day 1st of a 3-week cycle (n = 4), or IV gemcitabine 1250 mg/m^2 on days 1st, 8th and 15th of a 4-week cycle (n = 1)]; the ITT population comprised 70 randomized patients.
[c] Primary endpoint.

In Poland pixantrone is a new drug that is important in the treatment of refractory and recurrent aggressive malignant lymphomas such as DLBCL. Currently in Poland, the drug is reimbursed under the NFZ no B93 drug program.

References

1. Hübel K. An evaluation of pixantrone for the treatment of non-Hodgkin's lymphoma. Expert Opin Pharmacother. 2018; 19(16): 1829-34.
2. Minotti G, Menna P, Salvatorelli E. Do You Know Pixantrone? Chemotherapy. 2017; 62: 192-3. http://doi.org/10.1159/000464276.
3. NCBI Bookshelf. A service of the National Library of Medicine, National Institutes of Health.
4. Pixantrone – Benefit Assessment According to §35a Social Code Book V. Extract of Dossier Assessment No. A12-17 Version 1.0. Institute for Quality and Efficiency in Health Care. February 27, 2013.
5. Jamal-Hanjani M, Pettengell R. Pharmacokinetic evaluation of pixantrone for the treatment of non-Hodgkin's lymphoma. Expert Opin. Drug Metab Toxicol. 2011; 7(11): 1441-8.
6. Keating GM. Pixantrone: A Review in Relapsed or Refractory Aggressive Non-Hodgkin's Lymphoma. Drugs. 2016; 76: 1579-86.
7. Lekue CB, Cicala SG, Leppä S. Pixantrone beyond monotherapy: a review. Ann Hematol. 2019; 98: 2025-33.
8. Pixantron – charakterystyka produktu leczniczego.
9. Pettengell R, Coiffi B, Narayanan G et al. Pixantrone dimaleate versus other chemotherapeutic agents as a single-agent salvage treatment in patients with relapsed or refractory aggressive non-Hodgkin lymphoma: a phase 3, multicentre, open-label, randomised trial. Lancet Oncol. 2012; 13: 696-706.
10. Minotti G, Han H, Cattan V et al. Pixantrone: novel mode of action and clinical readouts. Expert Rev Hematol. 2018; 11(7): 587-96.

Conflict of interests:
None.

Financial support:
None.

Ethics:
The authors had full access to the data and take full responsibility for its integrity.
All authors have read and agreed with the content of the manuscript as written.
The paper complies with the Helsinki Declaration, EU Directives and harmonized requirements for biomedical journals.