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ORIGINAL ARTICLE

Critical concepts, practice recommendations, and research perspectives of pixantrone therapy in non-Hodgkin lymphoma: a SIE, SIES, and GITMO consensus paper

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Abstract

Objectives: In this paper, we present a review of critical concepts and research perspectives and produce recommendations on the optimal use of pixantrone in non-Hodgkin lymphoma (NHL) by group discussion from an expert panel appointed by the Italian Society of Hematology and the affiliate societies, Società Italiana di Ematologia Sperimentale and Gruppo Italiano Trapianto di Midollo Osseo. *Methods:* Recommendations were produced using the Delphi process. Scientific evidence on pixantrone efficacy was analyzed using Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) methodology in the areas where at least one randomized trial was published. The following key issues were addressed for practical recommendations: pixantrone monotherapy in aggressive relapsed or refractory non-Hodgkin B-cell lymphomas and toxicity risk management in patients candidates to pixantrone. *Results and conclusions:* After a balanced and value-oriented discussion, the panel agreed that the benefit/risk profile was in favor of pixantrone in the treatment of adult patients with multiply relapsed or refractory aggressive NHL B-cell lymphomas. Pixantrone was deemed to be contraindicated in patients with uncontrolled cardiovascular disease. Despite a low rate of cardiotoxicity of pixantrone reported in clinical trials, the panel recommended that all patients receiving pixantrone should undergo periodical cardiac monitoring.

Key words pixantrone; guidelines; non-Hodgkin lymphoma; GRADE methodology

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Pixantrone is a novel *aza*-anthracenedione that in preclinical settings showed a remarkable activity in lymphomas and leukemias (1, 2). On May, 2012, the European Medicines Agency (EMA) recommended the granting of a conditional marketing authorization for pixantrone for the treatment of patients with multiply relapsed aggressive NHL as monotherapy (3, 4). In the main study submitted for this application, a significant difference in response rate was observed in favor of pixantrone, supported by the results of secondary endpoints of median progression-free (PFS) and overall survival (OS) times (5).

Pixantrone now represents a major advance in the treatment of NHL; however, several uncertainties still remain on the optimal use of the drug in the approved indication, in particular on cardiotoxicity management. In addition, new questions are emerging on the use of the drug early in the treatment of NHL, as well as on its effectiveness as a combination therapy. In order to support the physicians in managing patients candidates to pixantrone, a consensus development conference project on pixantrone was convened under the sponsorship of the Italian Society of Hematology and the affiliate societies Società Italiana di Ematologia

Sperimentale and Gruppo Italiano Trapianto di Midollo Osseo.

Design and methods

Organization

Two chairmen (ST and GB) appointed a panel of seven experts, selected for their expertise in research and clinical practice of adult lymphoid malignancies or in clinical pharmacology, hereafter called expert panel (EP). A clinician with expertise in clinical epidemiology (GB) assured the methodological appropriateness of the process.

GRADE use for evidence appraisal

We performed a structured literature search for English-language publications using electronic databases such as MEDLINE (2005–2014), EMBASE (2005–2014), reviews including Cochrane Database of Systematic Reviews, and the Cochrane Controlled Trials Register. References in identified reports and reviews were screened to find additional relevant publications. Publications which measured efficacy of pixantrone in persons with malignant lymphomas with or without a comparison group were included. We used the Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) methodology to rate confidence in estimates of effect for each outcome (6).

The consensus process

During an initial meeting, the EP agreed on the areas of major concern in the use of pixantrone by generating and rank-ordering clinical key questions using the criterion of clinical relevance, that is, impact on the management of patients and risk of inappropriateness, through a Delphi process (7). The candidate key questions that ranked highest formed the set of issues of the present document. During the first of four meetings, the EP examined the current state of knowledge regarding pixantrone and was accounted for the results of pixantrone critical appraisal. Each panelist drafted statements that addressed the identified key questions, and the remaining panelists scored their agreement with those statements and provided suggestions for rephrasing. For exploiting this phase of the process, the EP was convened and three further consensus meetings were held in Bologna, Italy. The overall goals of the meetings were to reach a definite consensus over question-specific statements for which there was disagreement during the first-round postal phase. The nominal group technique was used by which participants were first asked to comment in round-robin fashion on their preliminary votes and then to propose a new vote (8).

Results

Preclinical and clinical pharmacology

Pixantrone differs from mitoxantrone due to removal of the hydroquinone moiety, insertion of a nitrogen heteroatom, and substitution of (ethylamino)-diethylamino for (hydroxyethylamino)-ethylamino side chains. Such chemical modifications cause important effects on pixantrone activity. In preclinical settings, pixantrone showed a limited efficacy in cellular or animal models of solid malignancies but proved remarkably active in lymphomas and leukemias. Pixantrone also showed pharmacodynamics that were different from mitoxantrone. Whereas mitoxantrone killed tumor cells through topoisomerase IIα inhibition and consequent formation of DNA double-strand breaks, pixantrone effects on topoisomerase IIα were qualitatively similar but quantitatively modest (9).

Pixantrone acts primarily by disrupting mitotic fidelity and segregation of genomic material. This is shown by the formation of lagging chromosomes, chromosomal bridges, micronuclei and multinucleated cells. Apoptosis occurs after 3–4 waves of aberrant mitoses and is accompanied by limited accumulation of DNA double-strand breaks (10). Pixantrone is also able to alkylate DNA and to cause formation of unusually long-lived adducts. This is favored by conjugation of pixantrone with formaldehyde that is formed in measurable amounts in many cancer cells (11). Cause-and-effect relations between persistent DNA damage and topoisomerase IIα-independent missegregation events are likely to occur; in fact, the mitotic checkpoint inhibitor, pChk1, enhances cellular effects of pixantrone (12).

Pixantrone-induced apoptosis is only in part relayed by p53 (12). This finding anticipates a potential activity of pixantrone in non-Hodgkin lymphomas that harbor loss-of-function p53 mutations (13, 14); it also confirms that differences exist between pixantrone and mitoxantrone, whose effects on topoisomerase IIα inhibition and DNA damage are relayed to apoptosis by p53 (15). Interestingly, however, recent studies maintain that pixantrone is a topoisomerase IIα inhibitor (16). Data scrutiny shows that pixantrone inhibited topoisomerase IIα at concentrations exceeding its plasma Cmax in lymphoma patients.

Clinical use of anthracyclines and mitoxantrone is limited by a dose-related cardiotoxicity. Because anthracyclines are eliminated incompletely from cardiac tissue, the risk of cardiotoxicity extends lifetime (17). Sequential exposure to subtoxic doses of different anthracyclines, or sequential exposure to an anthracycline and mitoxantrone, is therefore limited by the risk of precipitating cardiotoxicity. Structural similarities with mitoxantrone and intuitive classification in the large group of anthracycline-like drugs raised concerns that pixantrone caused cardiotoxicity but studies of anthracycline-naïve or anthracycline-pretreated laboratory animals

soon revealed that pixantrone was much less cardiotoxic than doxorubicin or mitoxantrone and did not aggravate cardiotoxicity in doxorubicin-pretreated animals (18).

Cardiotoxicity from anthracyclines and anthracenediones is a multifactorial event that may be caused by excess formation of reactive oxygen species and other free radicals, or by inhibition of the β-isoform of topoisomerase II; anthracyclines are also known to convert into long-lived toxic metabolites (15, 19). Postcrystallization studies of pixantrone–topoisomerase II β complexes, and functional assays (16) suggest that pixantrone would not target cardiac topoisomerase II β. In a translational model of human heart pre-exposed to doxorubicin, pixantrone did not produce free radicals but actually inhibited formation of the long-lived and toxic doxorubicin metabolite, doxorubicinol. In comparable settings, mitoxantrone did produce free radicals and lacked inhibition of doxorubicinol formation (20). Pixantrone generation of reactive oxygen species only occurs in cell free systems that adopt high drug concentrations (16).

All such findings provide additional evidence to conclude that pixantrone is different from mitoxantrone and anthracyclines.

Recommendations

Pixantrone monotherapy in aggressive relapsed or refractory non-Hodgkin B-cell lymphomas

Early phase I or phase II trials with pixantrone. The standard approach for adult patients with aggressive NHL not achieving a complete remission or relapsing after anthracycline-based induction and eligible for intensive treatment includes a salvage combination based on the anti-CD20 antibody rituximab (in CD20-positive NHL) and a non-cross-resistant platinum-containing regimen. The most used regimens are DHAP/DHAOX (dexamethasone, cytarabine, and cisplatin/oxaliplatin), ICE (ifosfamide, carboplatin, etoposide), or ESHAP (methylprednisolone, etoposide, cytarabine, cisplatin). Responders to re-induction usually undergo consolidation with high-dose therapy and autologous stem cell transplantation (ASCT); in selected cases, allogeneic stem cell transplantation (allo-SCT) may be considered. In the planning of treatment for patients in this setting, one of the trickiest issues that physicians have to face is progressive myocardial toxicity related to the cumulative, dose-dependent damage induced by anthracyclines, which may lead to congestive heart failure (CHF).

Pixantrone was synthesized to provide similar antitumor activity similar to the anthracyclines, but without the cardiotoxicity. Three phase I dose-escalation single-agent studies (two in solid tumors and one in NHL/chronic lymphocytic leukemia) explored two different treatment regimens with pixantrone monotherapy: pixantrone every 3 wk and pixantrone weekly for three consecutive weeks with 1-week rest (21–23). The final schedule selected for phase II development was 85 mg/m^2 of pixantrone on days 1, 8, and 15 of a 28-d cycle.

Following the promising results of pixantrone in earlier trials, pixantrone has been tested as a single agent in a prospective phase II study (24). Five patients achieved a complete remission (CR) (15%) and nine had a partial response (PR) (27%), with a median PFS of 106 d. Overall response rate (ORR) was higher than that reported for single-agent etoposide, cisplatin, or mitoxantrone.

Phase III randomized trial comparing pixantrone with single-agent chemotherapy. The only phase III trial was an international, multicenter, randomized, active-controlled, open-label study reported by Pettengell and coworkers (PIX 301) and it led to drug registration by the EMA (5). The study recruited patients with relapsed/refractory aggressive or transformed NHL refractory to at least two prior regimens, including at least one anthracycline-containing regimen (median cumulative dose of approximately 300 mg of doxorubicin equivalents/m^2). Patients were randomized (1 : 1) to receive either pixantrone (with dose and schedule identical to that used in the phase II setting) or single-agent chemotherapy of the investigators choice, some of them being: vinorelbine, ifosfamide, oxaliplatin, etoposide, gemcitabine, or mitoxantrone. The primary endpoints were CR and complete remission unconfirmed (CRu) with PFS and OS as secondary endpoints. The initial planned sample size was 320 patients, but the study was subsequently closed 3 yr after the first patient was enrolled, with only 140 patients randomized (70 per arm) due to very slow accrual. Most of the enrolled patients had diffuse large B-cell lymphoma (76% in the pixantrone arm vs. 73% in comparator arm) or transformed indolent lymphoma (14% vs. 13%), with a median age of 60 yr vs. 58 yr, mainly unfavorable Ann Arbor stage and International Prognostic Index (IPI) scores.

Patients living in countries where rituximab was available were only eligible if they had received rituximab therapy. A similar number of patients in each group had previously received rituximab. Baseline patient characteristics were well balanced in experimental and control arms. Seventy-one percent of patients in the experimental arm and 76% in the comparator arm did not complete the six planned cycles because of disease progression or relapse (41% in the pixantrone group vs. 58% in the comparator group) or adverse events (AEs) (22% vs. 13%, respectively). The response analysis, based on the intention-to-treat population, showed a benefit in terms of CR/CRu rate and ORR for pixantrone (20% vs. 5.7%, $P = 0.021$; 37.1% vs. 14.3%, $P = 0.003$, respectively). Median PFS was longer in the experimental arm (5.3 months vs. 2.6 months, $P = 0.005$), and a trend toward longer median OS was observed with pixantrone, but this was not statistically significant (10.2 months vs. 7.6 months, $P = 0.251$). An exploratory analysis was

performed to investigate whether any favorable factor predicting a better outcome was recognizable; an absence of prior anti-CD20 treatment or stem cell transplantation, less than three prior chemotherapy regimens, age ≥65 yr, and female sex were identified as favorable prognostic factors, but prior use of rituximab did not influence the benefit on PFS.

In terms of toxicity, patients in the experimental arm experienced more grade III and IV AEs (76.5% vs. 52.2%); however, the overall proportion of complications was similar in the two groups (97.1% vs. 91%). No evidence of cumulative, dose-related cardiotoxicity was reported, and decreases in left ventricular ejection fraction (LVEF) were not associated with clinical evidence of cardiac impairment.

Critical appraisal of evidence and panel discussion on appropriateness of pixantrone in advanced NHL. A critical appraisal of evidence resulting from the randomized open-label controlled clinical trial according to GRADE methodology (6) is reported in the Supplement material. Two main reasons for downgrading the quality of evidence supporting the use of pixantrone in relapsed or refractory NHL were highlighted. These were imprecision of the estimate of OS and indirectness of the population treated in the trial. As a matter of fact, the difference in OS between experimental arm and control arm was not statistically significant. Consequently, responders would not be judged responders using OS. This discordance, reflecting indirectness of the OS outcome measurement in the trial, could influence the confidence in the effect size measurement because a proportion of the responses were not clinically meaningful. Moreover, the EMA approval of pixantrone did not specify an exclusion for patients having previously received rituximab. Thus, entry criteria of the trial differed substantially from the EMA-approved therapy indication. Because of these two issues, the risk of indirectness in the population being considered for therapy is high.

These conclusions were provided to the EP for discussion. As far as imprecision in the estimate of OS, the EP reasoned that the study was powered to look at response rate (RR) and PFS (primary endpoints) and that, in the setting of patients with relapsed/refractory NHL, RR and PFS were deemed appropriate quality indicator of outcome. Thus, PFS may well be intended as a surrogate for OS. Moreover, the EP claimed that the real role of pixantrone therapy in multiply relapsed refractory NHL patients is the potential 'bridge' to SCT, rendering OS outcome not so critical for these patients in which the principal aim is to obtain a clinical response (CR-CRu) to lead the patient (if eligible) to a consolidation SCT. In the EP's opinion, the low precision level in the estimate of OS for pixantrone superiority over investigator's choice in rituximab-treated patients neither affects credibility of findings in PIX 301 study nor introduces concerns in using pixantrone as per EMA recommendation.

As far as the indirectness of the population, the EP agreed that the inclusion of rituximab-naïve patients in the study represented a bias in the quality of evidence of pixantrone activity. In fact, nowadays almost all patients would be expected to have received previous rituximab, and previous exposure to this antibody is known to be associated with a decreased RR to subsequent chemotherapy. However, the EP highlighted the evidence of poor outcome in the analysis of patients naïve and non-naïve to rituximab derived from a substudy, resulting in a very limited number of patients. Despite this small number of patients, the RR in those previously exposed to rituximab was 1.76 (95% CI, 0.77–3.98). This was not statistically significant but considered by the EP as clinically relevant. The EP agreed that the results in patients naïve to rituximab do not affect the overall credibility of findings in Pettengell's study. The EP also acknowledged that cost-effectiveness of pixantrone was positively evaluated by NICE and others (25, 26).

Recommendations. According to EMA, pixantrone is indicated for the treatment of adult patients with multiply relapsed or refractory aggressive NHL B-cell lymphomas.

The EMA approval was based on only one randomized trial whose evidence of the better benefit of pixantrone with respect to available therapies was judged moderate. In particular, the evidence on the risk/benefit risk profile of the drug was judged of lower quality in patients who had received a previous rituximab therapy.

After a balanced and value-oriented discussion, the panel agreed that the benefit/risk profile was in favor of pixantrone in any category of patients despite the previous treatment (recommendation of moderate strength).

Toxicity risk management in patients candidates to pixantrone

During treatment with pixantrone as single agent in relapsed aggressive NHL, grade 3–4 leukopenia and neutropenia were the most relevant hematological toxicity (5, 24). These were generally brief, lasting a median of 7.5 d, and did not increase with the number of cycles, whereas grade 3–4 anemia or thrombocytopenia was rarely observed. In particular, in the Pettengels's trial (5), grade III–IV neutropenia was more common in patients treated with pixantrone (41.2% vs. 19.4%), as was febrile neutropenia (7.4% vs. 3.0%), while the rate of thrombocytopenia was similar and that of anemia was lower (11.8% vs. 10.4% and 5.9% vs. 13.4%, respectively).

In the open-label, non-randomized, non-comparative phase II study (24), only three patients, two of whom with a previous low value of (LVEF), showed a ≥10% decrease in LVEF measured by multigated acquisition scan. In one of these, the treatment had to be discontinued when the patient developed cardiac symptoms and LVEF decreased to 25%. All of patients with cardiovascular toxicity were more than 65 yr of age and had received a prior anthracycline.

In the pivotal phase III trial (5), cardiac toxicity was closely monitored, and a higher incidence of cardiac events was seen in the pixantrone group (35% vs. 21%). Only 13% cases of cardiac events were considered related to pixantrone, and all were asymptomatic decreases in LVEF. No clear cases of pixantrone-associated CHF were reported, and importantly, cardiac events did not correlate with the cumulative dose of pixantrone. This latter finding denoted differences between pixantrone and anthracyclines, whose cardiotoxicity typically develops in a dose-related manner. Five patients in the experimental arm had a previous history of CHF or continuing cardiomyopathy at the time of enrollment, whereas none of the patients in the comparator group had a history of these conditions. Such an unbalanced representation of cardiac risk factors in the two study arms could have at least in part contributed to the observed higher incidence of cardiac adverse events in patients randomized to pixantrone. Overall, pixantrone cardiotoxicity is judged to be acceptable, especially if one appreciates that patients had been previously exposed to a median cumulative doxorubicin dose of approximately 300 mg/m^2. The acceptable cardiotoxicity of pixantrone is confirmed by the Periodic Safety Report (PSUR) that summarizes pixantrone safety data from both clinical and commercial data, the vast majority of cardiac events attributed to pixantrone being coded 'investigations' (ejection fraction decreased) rather than cardiac disorders (27).

Clinical and health conditions more frequently related to cardiovascular events during pixantrone administration are the age greater than 65 yr, the low LVEF value before therapy, the previous history of CHF, and cardiomyopathy.

No evidence was reported for the efficacy of cardiovascular prophylaxis in patients candidates to pixantrone and carrying these risk factors. No recommendations for prophylaxis or treatment of cardiac toxicity were reported.

Recommendations

The EP agreed that neutropenia ensuing after pixantrone single-agent therapy should be managed by G-CSF prophylaxis as for other NHL chemotherapy regimens (28).

Pixantrone is contraindicated in patients with uncontrolled cardiovascular disease.

All patients without cardiovascular disease or with a controlled cardiovascular disease who are candidates for pixantrone therapy should undergo a cardiological evaluation including electrocardiogram and echocardiogram. There are no indications to cardiovascular prophylaxis in patients without cardiovascular disease.

In patients on treatment for cardiovascular disease, the appropriateness of cardiovascular therapy should be verified before pixantrone therapy.

Despite a low rate of cardiotoxicity of pixantrone reported in clinical trials, the EP recommended that all patients receiving pixantrone should undergo periodical cardiac monitoring.

If cardiac toxicity is demonstrated during treatment (grade two cardiac toxicity (29) or significant decrease in LVEF), the individual risk/benefit ratio of continuing pixantrone therapy should be evaluated.

Research perspectives

Pixantrone combination therapy in relapsed or refractory non-Hodgkin B-cell lymphomas

Four studies have investigated pixantrone as part of a polychemotherapeutic regimen, in patients with relapsed NHL. Three studies included patients with aggressive NHL, and one study included patients with indolent NHL. Three studies were reported in full papers while one in abstract form (30–33) (Table 1). Taken overall, the responses ranged from 58% to 73%. Cardiotoxicity rates ranged from 7% to 19% with limited grade II-IV toxicities (2–3%). These results

Table 1 Studies using pixantrone in combination therapy for patients with refractory or resistant aggressive NHL

Study	Design	Combination	Number of patients treated	Media number of cycles administered	ORR, *n* (%)	CR, *n* (%)	PR, *n* (%)	Median PFS	OS
Lim *et al.*, (2007) (30)	Phase I/II	PSHAP	19	4 (1–6)	11 (58)	7 (37)	4 (21)	5.7 months	Median: 14.7 months
Borchman *et al.*, (2011) (31)	Phase I/II	CPOP	65	6 (1–6)	47 (72)	30 (46)	17 (26)	8.2 months	Median: 17.9 months
d'Amore *et al.*, (2014) (32)	Preliminary clinical experience	PREBEN/ PEBEN	8	3 (2–6)	6 (62.5)	3 (37.5)	2 (25)		
Srokowski *et al.*, (2011) (33)	Dose-escalation phase I study	FPD-R	27	5 (1–8)	19 (70)	12 (44)	7 (26)		2 and 3-yr: 91.5%

PSHAP, pixantrone, methylprednisolone, high-dose cytarabine, cisplatin; CPOP, cyclophosphamide, pixantrone, vincristine, prednisone; FPD-R, fludarabine, pixantrone, dexamethasone, rituximab; PREBEN/PEBEN, etoposide, bendamustine, pixantrone (±rituximab).

suggest that pixantrone can be further evaluated in combination studies.

Ideal candidates for combination therapy with pixantrone in NHL should target molecular pathways other than those of pixantrone or should be able to remove molecular barriers to the action of pixantrone. Combination agents and pixantrone would therefore elicit synergistic rather than additive effects in tumor cells. The finding that clinically relevant concentrations of pixantrone lacked inhibition of topoisomerase IIα anticipates that non-anthracycline topoisomerase IIα inhibitors would synergize with pixantrone in tumor cells. The epipodophyllotoxin, etoposide, is a general topoisomerase inhibitor that should be considered for combination with pixantrone. Other combination strategies might adopt inhibitors of mitotic checkpoints. The mixed antimetabolite alkylator, bendamustine, warrants consideration as it induces a complex stress response that downregulates the activity of numerous mitotic checkpoints (34).

Among the combination therapies including pixantrone, only one trial fitted this rationale. d'Amore and coworkers (32) explored a combination chemotherapy regimen based on pixantrone in patients with multiply relapsed or refractory aggressive B and T non-Hodgkin lymphoma in which etoposide and bendamustine were chosen as companion compounds. Rituximab was added in patients with B-cell lymphoma. The adapted schedule consisted of pixantrone 50 mg/m^2 i.v. day 1 + 8, etoposide 100 mg i.v. day 1, bendamustine 90 mg/m^2 i.v. day 1 with or without the addition of rituximab 375 mg/m2 i.v. day 1 (PREBEN/PEBEN). If feasible, each cycle was given at 3-weekly intervals for a maximum of six cycles. Three patients (25%) achieved a CR and 2 (50%) obtained a partial response (ORR 62.5%). One trial with ongoing enrollment is registered on *ClinicalTrials.gov* (NCT 01491841) aimed at testing bendamustine, rituximab, and pixantrone in a phase I/II trial in patients with relapsed/refractory B-cell NHL.

Two other relevant trials are registered on the *ClinicalTrials.gov* website, both concerning the treatment of relapsed refractory B-cell NHL. The first study investigates relapsed diffuse large B-cell lymphoma, transformed from indolent lymphoma, and follicular grade III lymphoma not eligible for SCT. This phase III, multicenter, randomized trial is comparing a pixantrone–rituximab regimen with a gemcitabine–rituximab regimen, with a planned sample size of 350 patients (NCT01321541). The second one was aimed to evaluate the ORR of obinutuzumab (GA101) in combination with pixantrone. Seventy patients will receive up to six cycles of the regimen. (NCT02499003).

Pixantrone combination therapy in untreated DLBC lymphoma

Herbrecht and coworkers initiated a phase II multicenter, randomized controlled trial in untreated patients with stage II-IV DLBCL substituting doxorubicin with pixantrone (150 mg/m^2) in R-CHOP (R-CPOP) (35). After four cycles, patients with a (PR) received four more cycles of treatment; those with CR received two more cycles. The primary objective of the trial was to show non-inferiority of R-CPOP to R-CHOP, and secondary endpoints included ORR, PFS, OS, and safety. The study recruited 124 from the preplanned 280 patients needed, due to financial constraints. Of the 124 patients enrolled, 61 were randomized to R-CPOP and 63 to R-CHOP. In terms of efficacy, there were no statistically significant differences between the two regimens. CR rate in the intent-to-treat population was 72.1% for R-CPOP vs. 79.4% for R-CHOP, and ORR was 82% vs. 87.3%. Median PFS was not reached in the CPOP-R arm and was 40 months in the CHOP-R arm; median OS was not reached in either treatment arm. OS rates were lower for patients treated with CPOP-R (hazard ratio 2.37, $P = 0.029$), with more deaths occurring in the CPOP-R arm (30% vs. 14%). Overall, AEs were similar in approximately 85% of patients in both arms. Non-inferiority could not be demonstrated due to early closure of the trial due to financial constraints. Despite this, efficacy was comparable between the two arms, but R-CPOP showed a reduced cardiotoxicity measured by echocardiography or circulating levels of troponin.

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