Case Report



# The relationship between PARP inhibitors with the relapse and leukemisation of lymphomas: a case report

**Marta Navalón-Jiménez[1,2#], Alejandro Olivares-Hernández[1,2#], Luis Figuero-Pérez[1,2], José Pablo Miramontes-González[3,4], Enrique Montero-Mateos[5], Juan Jesús Cruz-Hernández[1,2,6], Emilio Fonseca-Sánchez[1,2,6]**

[1]Department of Medical Oncology, University Hospital of Salamanca, Salamanca, Spain; [2]Biomedical Research Institute of Salamanca, Salamanca, Spain; [3]Department of Internal Medicine, University Hospital Rio Hortega, Valladolid, Spain; [4]Faculty of Medicine, University of Valladolid, Valladolid, Spain; [5]Department of Pathology, University Hospital of Salamanca, Salamanca, Spain; [6]Faculty of Medicine, University of Salamanca, Salamanca, Spain

*Contributions:* (I) Conception and design: A Olivares-Hernández, M Navalón-Jiménez; (II) Administrative support: E Fonseca-Sánchez, JJ Cruz-Hernández; (III) Provision of study materials or patients: A Olivares-Hernández, L Figuero-Pérez, E Montero-Mateos; (IV) Collection and assembly of data: A Olivares-Hernández, L Figuero-Pérez, JP Miramontes-González; (V) Data analysis and interpretation: A Olivares-Hernández, JP Miramontes-González; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this work.

*Correspondence to:* Alejandro Olivares-Hernández, MD. Department of Medical Oncology, Paseo San Vicente, 182, 37007, Salamanca, Spain. Email: aolivares@saludcastillayleon.es.

**Background:** Nowadays the poly-ADP ribose polymerase inhibitors (iPARPs) are the mainly treatment for the ovarian cancer and other solid tumours. However, given its recent use, long-term toxicity is still under study. The occurrence of acute leukaemias and myelodysplastic syndromes (MDS) secondarily to iPARPs is known (0.5–1%).

**Case Description:** We present the case of a 78-year-old patient with a serous carcinoma of ovary in maintenance treatment with Niraparib after response to platinum. Along with the ovarian carcinoma the patient developed a diffuse large cell B lymphoma (DLBCL) five years ago, treated with R-CHOP (Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, Prednisolone) with complete response. The patient was evaluated in the emergency due to constitutional syndrome, objectifying a bicytopenia (platelets 28,000/mcL, haemoglobin 9.6 g/dL). In the study of bicytopenia, a bone marrow infiltration by high-grade B lymphoma was diagnosed.

**Conclusions:** The action of iPARPs on the selection of acquired mutations in clonal haematopoiesis maybe have been able to accelerate the process of relapse and leukemisation of the previous lymphoma. The association of treatment with iPARPs and the development of lymphomas is key for increasing knowledge of the safety profiles these drugs.

**Keywords:** Poly-ADP ribose polymerase inhibitor (iPARP); lymphomas; leukemisation; relapse; case report

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## Introduction

The treatment of tumours with homologous recombination deficit has undergone a radical change in recent years. The introduction of the treatment of ovarian carcinomas using poly-ADP ribose polymerase inhibitor (iPARP) has led to increased survival and response rates in these tumours (1). Different clinical trials, such as SOLO-1 and PRIMA, have shown that progression-free survival (PFS) and disease control rates are much higher in those patients receiving

**Table 1** Results from the emergency laboratory

| Determination | Results | Laboratory range |
|---|---|---|
| Glucose | 121 (mg/dL) | 76–110 (mg/dL) |
| Creatinine | 2.49 (mg/dL) | 0.5–0.9 (mg/dL) |
| Calcium | 9.6 (mg/dL) | 8.8–10.2 (mg/dL) |
| Sodium | 134 (mmol/L) | 135–145 (mmol/L) |
| Potassium | 4.4 (mmol/L) | 3.5–5.1 (mmol/L) |
| Total bilirubin | 0.45 (mg/dL) | 0.15–1.2 (mg/dL) |
| C-reactive protein | 3.19 (mg/dL) | 0–0.5 (mg/dL) |
| Haemoglobin | 9.6 (g/dL) | 12–16 (g/dL) |
| Leukocytes | 14.490 (/mcL) | 4.5–10.8 (/mcL) |
| Neutrophil | 9.250 (/mcL) | 1.4–6.5 (/mcL) |
| Platelets | 28.000 (/mcL) | 150–450 (/mcL) |
| pH | 7.34 | 7.35–7.45 |
| Lactate | 4.8 (mmol/L) | 0.5–1.6 (mmol/L) |

maintenance therapy with iPARPs after platinum response (2,3). Although tolerance to these drugs is usually good, haematological toxicity is one of their main limitations. The occurrence of acute leukaemias and myelodysplastic syndromes (MDS) secondarily to iPARPs is known and has been identified in 0.5–1% of patients (4,5); however, there are no data on, nor associations with, the appearance or alteration of the course of the lymphomas described. In this report, we aim to assess the association of iPARPs with the development of lymphomas through the clinical case of a patient who suffered a relapse and transformation of leukaemia from a lymphoma in complete response after treatment with iPARP for ovarian carcinoma. We present the following article in accordance with the CARE reporting checklist (available at https://acr.amegroups.com/article/view/10.21037/acr-22-91/rc).

### Highlight box

**Key findings**

- Possible increased of risk of lymphoma development with iPARP treatment.

**What is known and what is new?**

- The association between the risk of developing MDS or leukaemias with iPARP treatment is already known and described
- The increased risk of lymphoma development with iPARP is unknown.

**What is the implication, and what should change now?**

- Given the alterations in haematopoiesis caused by iPARPs and the possible increased risk of lymphoma development, if these findings are confirmed, closer monitoring of these patients would be necessary.

## Case presentation

We present the case of a 78-year-old woman with a diagnosis of serous carcinoma of the ovary who was undergoing maintenance treatment with Niraparib. The patient was diagnosed in 2011 with stage IIIC serous ovarian carcinoma (unmutated somatic *BRCA*). After receiving a neoadjuvant with Paclitaxel-Carboplatin, the patient underwent surgery with R0 resection. Subsequently, she suffered two tumour recurrences at the pelvic level, in 2014 and 2019, both of which were treated with surgery (both R0 interventions) plus adjuvant chemotherapy. In the second of them, after a complete response, maintenance treatment with Niraparib was prescribed. It began in January 2020. In 2016, during follow-up on the second relapse, in 2014, the patient was diagnosed with diffuse large cell B lymphoma (DLBCL). She received treatment with an R-CHOP scheme for six cycles with complete response without recurrence or incidents in subsequent follow-up.

In March 2021, the patient sought treatment for a clinical evaluation of constitutional syndrome with abdominal pain. After performing the physical examination, during which no alterations were observed, an urgent blood test was conducted, and the presence of a bicytopenia (platelets 28,000/mcL, haemoglobin 9.6 g/dL) of unknown origin with an acute deterioration of renal function of prerenal origin was observed (*Table 1*). An urgent abdominal CT scan was requested, and a peritoneal carcinomatosis with free fluid secondary to ovarian tumour recurrence was observed. It was decided to admit the patient for transfusion support and a study of the bicytopenia. Erythroblastosis was observed in the requested blood smear, with signs compatible with bone marrow infiltration. After that, a bone marrow biopsy was performed. The anatomo-pathological results were compatible with bone marrow infiltration by high-grade B lymphoma (*Figure 1*), no other lesions compatible with medullary involvement by ovarian carcinoma were observed.

After the previous diagnosis, the patient developed an infection without focus (negative cultures and imaging tests), leading to the need for greater transfusion support

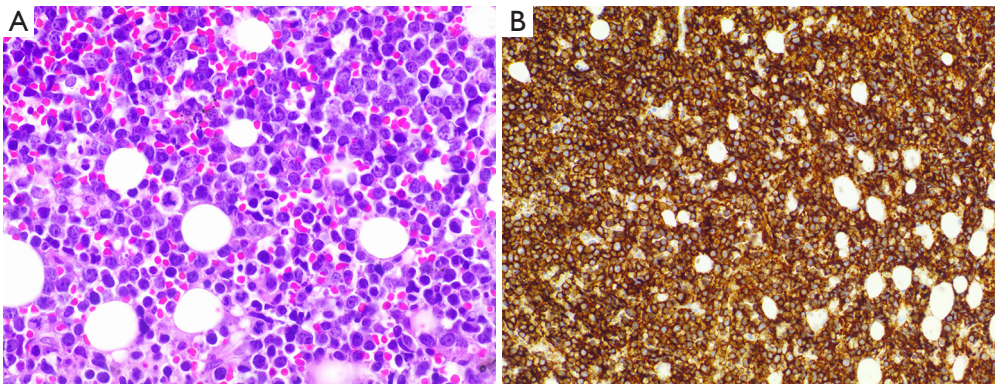


**Figure 1** Histopathological and immunohistochemical features of the bone marrow biopsy. (A) Haematoxylin and eosin section showing a proliferation of large-sized lymphoid cells with large nuclei and conspicuous nucleoli (400× magnification). (B) Positive for CD20 (400×).

in the forms of both blood and platelets. Treatment with piperacillin-tazobactam plus teicoplanin was initiated, and an evacuatory paracentesis was performed to improve renal function with diuretic treatment. Despite the measures in place, the patient died prior to the start of treatment for the lymphoid tumour.

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

## Discussion

The association between acute leukaemia and MDS with iPARPs is described in virtually all cases of ovarian carcinomas. The theoretical mechanism proposed for this relationship is derived from the possible action of iPARPs on the selection of acquired mutations in clonal haematopoiesis in the DNA damage response pathway (6). The risk factors that predict the possible development of these haematological alterations are not known; however, there are several hypotheses that relate the germinal mutations of *BRCA1/2*, *TP53* or *PALB2* with an increased risk of developing acute leukaemia or MDS (7,8).

In the case of our patient, there was a relapse with laeukemisation of DLBCL five years after the complete response to the R-CHOP scheme. The possibility of the existence of acquired mutations in pathological lymphoid cells that will lead to an increase in the probability of recurrence and greater aggressiveness of DLBCL is key. Treatment with Niraparib resulted in a 14-month PFS with no grade 3–4 toxicity. This is why the long exposure to iPARPs in this patient led to an increase in inadequate clonal haematopoiesis and the consequent lymphoid tumour recurrence (9). The early detection of cases at risk for the development of haematological alterations with iPARPs would allow a premature stopping of treatment with iPARP, or a different action in the follow-up protocols, for these patients. In addition to the iPARP treatment, the patient in this case had previously received multiple chemotherapy treatments (R-CHOP and Paclitaxel-Carboplatin), which may have led to an increase in haematopoiesis alterations, increasing the likelihood of recurrence of the haematological malignancy together with the iPARPs.

Although iPARP treatment has been associated with the development of MDS and leukaemias, its association with lymphomas is less clear. However, there are data supporting the association in the case of our patient. In the real-world data study by Zhao *et al.* (10), the latency period between the onset of iPARP and the onset or recurrence of haematological malignancy is like our case. Furthermore, a large percentage of cases presented as highly aggressive neoplasms with a high rate of fatal events. Therefore, although the association is novel, it is highly similar to cases of MDS and leukaemia.

## Conclusions

In conclusion, the association of treatment with iPARP and the development of lymphomas is key for increasing knowledge of the safety profiles these drugs. The search for risk factors associated with the development of

haematological neoplasms secondary to iPARP is essential for the future prevention of these pathologies in cancer patients.

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## Footnote

*Reporting Checklist:* The authors have completed the CARE reporting checklist. Available at https://acr.amegroups.com/article/view/10.21037/acr-22-91/rc

*Conflicts of Interest:* All authors have completed the ICMJE uniform disclosure form (available at https://acr.amegroups.com/article/view/10.21037/acr-22-91/coif). The authors have no conflicts of interest to declare.

*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.



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