Rucaparib versus standard-of-care chemotherapy in patients with relapsed ovarian cancer and a deleterious BRCA1 or BRCA2 mutation (ARIEL4): an international, open-label, randomised, phase 3 trial

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1. 簡述論文的概要以及重大發現

卵巢癌是復發性很高的癌症，當復發或轉移之後進入末期之後，治療選擇很少，而且治療的風險也很大。因此，開發針對疾病分子特徵的標靶治療，提高復發性卵巢癌治療的效果。

Rucaparib 是一種 PARP 抑制劑，可以阻斷癌細胞內有受損 BRCA 基因的雙股 DNA 斷裂不被修復，導致細胞死亡。Rucaparib 在美國和歐洲已被批准為 BRCA1 或 BRCA2 突變，復發性卵巢癌患者的單一療法治療。在這個研究中，作者想要比較 rucaparib 標靶藥物與化療藥物的治療效果。

這篇研究證明雖然在病患群體中，rucaparib 與化療的實體腫瘤反應評估沒有差異，但在使用 rucaparib 的病患無進展存留期比較長，這可能反映了使用 rucaparib 的人，可以延長她們的疾病穩定性。

2. 對論文內容的提問

要使用標靶藥物和化療藥物前，要先經過 2 次或 2 次以上的化療，才繼續後續的研究，那之後用藥產生的不良反應結果，是否有可能因先前化療次數多寡有所影響？

3. 論文的缺點與評論

這篇論文是設計從 12 個國家招募病患，想要比較族群多樣性治療效果，但大多數患者來自中歐和東歐，病患群體的分佈可能不被認為是種族多樣性。

雖然健保有給付 PARP 抑制劑的費用，但是做基因檢測還有使用藥物後的不適應症，都需要病人自費，每個月可能要花幾十萬，費用過高。

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Summary

Background Few prospective studies have compared poly(adenosine diphosphate-ribose) polymerase (PARP) inhibitors to chemotherapy for the treatment of *BRCA1*-mutated or *BRCA2*-mutated ovarian carcinoma. We aimed to assess rucaparib versus platinum-based and non-platinum-based chemotherapy in this setting.

Methods In this open-label, randomised, controlled, phase 3 study (ARIEL4), conducted in 64 hospitals and cancer centres across 12 countries (Brazil, Canada, Czech Republic, Hungary, Israel, Italy, Poland, Russia, Spain, Ukraine, the UK, and the USA), we recruited patients aged 18 years and older with *BRCA1*-mutated or *BRCA2*-mutated ovarian carcinoma, with an Eastern Cooperative Oncology Group performance status of 0 or 1, and who had received two or more previous chemotherapy regimens. Eligible patients were randomly assigned (2:1), using an interactive response technology and block randomisation (block size of six) and stratified by progression-free interval after the most recent platinum-containing therapy, to oral rucaparib (600 mg twice daily) or chemotherapy (administered per institutional guidelines). Patients assigned to the chemotherapy group with platinum-resistant or partially platinum-sensitive disease were given paclitaxel (starting dose 60–80 mg/m² on days 1, 8, and 15); those with fully platinum-sensitive disease received platinum-based chemotherapy (single-agent cisplatin or carboplatin, or platinum-doublet chemotherapy). Patients were treated in 21-day or 28-day cycles. The primary endpoint was investigator-assessed progression-free survival, assessed in the efficacy population (all randomly assigned patients with deleterious *BRCA1* or *BRCA2* mutations without reversion mutations), and then in the intention-to-treat population (all randomly assigned patients). Safety was assessed in all patients who received at least one dose of assigned study treatment. This study is registered with ClinicalTrials.gov, NCT02855944; enrolment is complete, and the study is ongoing.

Findings Between March 1, 2017, and Sept 24, 2020, 930 patients were screened, of whom 349 eligible patients were randomly assigned to rucaparib (n=233) or chemotherapy (n=116). Median age was 58 years (IQR 52–64) and 332 (95%) patients were White. As of data cutoff (Sept 30, 2020), median follow-up was 25·0 months (IQR 13·8–32·5). In the efficacy population (220 patients in the rucaparib group; 105 in the chemotherapy group), median progression-free survival was 7·4 months (95% CI 7·3–9·1) in the rucaparib group versus 5·7 months (5·5–7·3) in the chemotherapy group (hazard ratio [HR] 0·64 [95% CI 0·49–0·84]; p=0·0010). In the intention-to-treat population (233 in the rucaparib group; 116 in the chemotherapy group), median progression-free survival was 7·4 months (95% CI 6·7–7·9) in the rucaparib group versus 5·7 months (5·5–6·7) in the chemotherapy group (HR 0·67 [95% CI 0·52–0·86]; p=0·0017). Most treatment-emergent adverse events were grade 1 or 2. The most common grade 3 or worse treatment-emergent adverse event was anaemia or decreased haemoglobin (in 52 [22%] of 232 patients in the rucaparib group *vs* six [5%] of 113 in the chemotherapy group). Serious treatment-emergent adverse events occurred in 62 (27%) patients in the rucaparib group versus 13 (12%) in the chemotherapy group; serious adverse events considered related to treatment by the investigator occurred in 32 (14%) patients in the rucaparib group and six (5%) in the chemotherapy group. Three deaths were considered to be potentially related to rucaparib (one due to cardiac disorder, one due to myelodysplastic syndrome, and one with an unconfirmed cause).

Interpretation Results from the ARIEL4 study support rucaparib as an alternative treatment option to chemotherapy for patients with relapsed, *BRCA1*-mutated or *BRCA2*-mutated ovarian carcinoma.

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See Comment page 440

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