Evaluation of maintenance treatment with PARP inhibitors in ovarian carcinoma patients responding to platinum therapy: Use of restricted mean survival time as an index of efficacy

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Abstract. Background: Maintenance therapy using poly (ADP-ribose) polymerase inhibitors (PARPIs) is an important therapeutic option in advanced ovarian cancer after platinum-based chemotherapy. Materials and methods: We evaluated randomized studies (n = 5) describing the effect of maintenance therapy with PARPIs; they were obtained mainly by searching PubMed. Patient data for the analysis were derived from progression-free survival curves. Restricted mean survival time (RMST) and 95% confidence interval were estimated for individual arms of each trial. Results: The three PARPIs used (olaparib, niraparib, rucaparib) all showed a higher effectiveness than placebo. The gains in progression-free survival were 6 – 8 months. Conclusion: Maintenance therapy studies provide evidence that olaparib, niraparib, rucaparib are effective treatments for advanced ovarian cancer.

What is known about this subject
– Maintenance therapy with poly (ADP-ribose) polymerase inhibitors (PARPIs) is safe and effective in patients with advanced ovarian cancer responsive to platinum-based chemotherapy
– The hazard ratio (HR) and the median are the two most commonly used parameters for comparing time-to-event survival curves, despite several methodological limitations.
– Compared with the HR and the median, the restricted mean survival time (RMST) can be helpful to better analyze time-to-event curves.

What this study adds
– This is the first study to compare through a RMST analysis the effectiveness of different PARPIs as maintenance treatment.
– Our study gives more robust information on the survival gain of these treatments than that provided by HR and medians.
– The three PARPIs used (olaparib, niraparib, rucaparib) all had a higher effectiveness than placebo.
Introduction

The literature on the effectiveness of treatments for advanced ovarian cancer includes several randomized trials in which poly (ADP-ribose) polymerase inhibitors (PARPIs) have been proposed as maintenance therapy after platinum-based chemotherapy [1, 2, 3, 4, 5, 6]. Using the hazard ratio (HR) of progression-free survival (PFS) as outcome measure, some network meta-analyses (NETMAs) have already investigated the efficacy and safety of PARPIs (e.g., Gong et al. [7]). However, despite its wide use, the HR has important methodological limitations, such as its nature of being a relative parameter (not expressed in months) and its assumption of proportional risks over the entire follow-up of patients [8, 9, 10]. On the other hand, the restricted mean survival time (RMST) is increasingly recognized as a better methodological option to evaluate survival [8, 9, 10]. For this reason, we aimed the present study at examining, based on the RMST, the randomized controlled studies (RCTs) published on this topic.

Materials and methods

We carried out a literature search to identify the RCTs eligible for our analysis. This search was conducted in PubMed (last query on March 19, 2021) and covered the period from January 2010 to present date. A combined search term “(olaparip OR rucaparip OR niraparip) AND “ovarian carcinoma”” [please check quotation marks and parentheses] was employed along with the filter “randomised controlled trials”. Trial selection was represented according to the Preferred Reporting Items for Systemic Review and Meta-Analyses (PRISMA) approach [11]. We also searched the Cochrane Library for any recent systematic review on the subject, the ClinicalTrials.gov database, and the websites of European Medicines Agency (EMA) and U.S. Food and Drug Administration (FDA). The above keywords were employed also for these additional searches.

Our analysis included the trials that met the following criteria: a) advanced ovarian cancer treated with platinum-based chemotherapy; b) randomized design; c) treatment arm receiving olaparib, rucaparib, or niraparib; d) determination of PFS with a follow-up of at least 2 years. For each trial, we ex-
tract the basic information needed for our analysis; information on disease condition at baseline was recorded as well.

In all included trials, the endpoint of PFS was presented through a Kaplan-Meier curve. In analyzing each treatment arm of each study, we first reconstructed patient-level data from the Kaplan-Meier curve. This allowed us to determine the RMST according to an R-platform procedure. To extend the analysis of PFS over a lifetime horizon, we also applied mean lifetime survival (MLS) analysis to the same curves. MLS was based on the Weibull distribution. Indirect comparisons across individual PARPIs (as well as a network meta-analysis (NETMA)) were planned in the design of our analysis, but no NETMA was carried out for the reason outlined below.

Finally, detailed references about the above-mentioned statistical methods are reported in a preprint published by Messori [12].

Results

Our literature search extracted a total of 30 eligible papers; 5 RCTs met our inclusion criteria [1, 2, 3, 4, 5]. The PRISMA schematic is reported in the Supplemental material (Supplemental Figure S1 ●●● Not in the manuscript). Table 1 and Figure 1 report the values of RMST estimated from the 5 trials, with milestone set at 24 months. The gains in PFS determined by PARPIs in comparison with placebo showed some differences across the different agents and ranged from 5.63 months for niraparib vs. placebo in the trial by González-Martín et al. [4] to 8.08 months for niraparib vs. placebo in the trial by Mirza et al. [1].

The presence of two favorable prognostic characteristics (1. treatment administered as frontline setting (indicated as 1L in green [●●●Text has to be changed in case of black-and-white print]) as opposed to treatment in relapsed patients; 2. patients with BRCA mutation (indicated as MUT in green [●●●Text has to be changed in case of black-and-white print]) as opposed to non-BRCA mutated or undetermined BRCA status) likely influenced the values of RMST. This is particularly evident for the trial by Moore et al. [5] in which both favorable characteristics were present; accordingly, both the treatment group of this trial and the controls fared particularly well in terms of PFS. More importantly, these differences explain our choice of not using a NETMA to combine these results.

Finally, the values of MLS (Table 1) offer another perspective on the gain that can be expected from these agents; however, variability in MLS was wide likely because the true follow-up of these patients was limited to only 24 months.

Conclusion

Our results generated an updated synthesis on the effectiveness of the maintenance treatment with PARPIs. These findings clearly indicated that the three PARPIs performed better than placebo, and the greatest gain in PFS was found for rucaparib and olaparib. On the other hand, the information emerging from our study is that the values of RMST likely depend on the presence of favorable prognostic characteristics in the patients enrolled; hence, differences in effectiveness across the three agents can reasonably be ruled out. In comparison with the wide literature overview reported in Gong et al.’s [7] NETMA, our analysis is more specifically focused on the three agents already available in most Western countries. Our results have some methodological advantages

Figure 1. Values of restricted mean survival estimated for the 10 patient cohorts enrolled in the 5 randomized controlled trials. The presence of two favorable prognostic characteristics is reported for individual trials: 1. treatment administered as frontline setting (indicated as 1L in green [●●●Text has to be changed in case of black-and-white print]) as opposed to treatment in relapsed patients; 2. patients with BRCA mutation (indicated as MUT in green [●●●Text has to be changed in case of black-and-white print]) as opposed to non-BRCA mutated or undetermined BRCA status. Vertical bars represent 95% confidence interval.
because the RMST was used as outcome measure rather than the HR. For example, expressing the improvement of PFS in terms of absolute gain is a better choice than using a relative outcome measure such as the HR. Furthermore, a narrative approach was preferred in presenting our analysis because a NETMA tends to be contraindicated when the clinical material is inhomogeneous in some important characteristics.

The RMST plays an important role in interpreting findings where medians and HR do not clarify the clinical relevance of the difference between treatments. These situations are frequent, particularly in oncology. For example, in second-line treatment of HER2-positive breast cancer after progression with trastuzumab [13], interpreting the differences across lapatinib plus capecitabine, capecitabine monotherapy and trastuzumab emtansine could benefit from the application of the RMST [14].

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•••Author please complete.

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Conflict of interest

The authors declare no conflicts of interest.

References


