Gynecologic Oncology xxx (2018) xxx–xxx

Contents lists available at ScienceDirect

Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno

Review Article

The poly (ADP ribose) polymerase inhibitor niraparib: Management of toxicities

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HIGHLIGHTS

- Niraparib is a once daily PARP inhibitor with demonstrated efficacy as a maintenance agent.
- Toxicities include gastrointestinal, cardiovascular and hematologic toxicities, thrombocytopenia in particular
- Women <77 kg or baseline platelet count <150 K/μL are at a higher risk of grade 3/4 thrombocytopenia.

ARTICLE INFO

Article history:
Received 4 December 2017
Received in revised form 8 January 2018
Accepted 12 January 2018
Available online xxxx

Keywords:
PARP
Niraparib
Thrombocytopenia
Toxicity

ABSTRACT

Niraparib is an oral poly(ADP ribose) polymerase (PARP) inhibitor that is currently approved by the United States Food and Drug Administration (US FDA) as well as recently approved by the European Medicines Agency (EMA) for the maintenance treatment of women with recurrent ovarian cancer who are in complete or partial response to platinum-based chemotherapy. The mechanisms of action of niraparib include inhibition of PARP enzymatic activity as well as increased formation of PARP-DNA complexes through "trapping" the PARP enzyme on damaged DNA. Phase I and III studies have demonstrated activity and benefit of niraparib in both *BRCA* mutated (*BRCA*m) and *BRCA* wild-type (*BRCA*wt) cancers. Phase I testing of niraparib established the maximally tolerated dose of 300 mg by mouth (PO) daily, and the phase 3 ENGOT-OV16/NOVA study demonstrated the benefit of niraparib maintenance therapy compared to placebo after completion of and response to platinum-based chemotherapy in both *BRCA*m and *BRCA*wt ovarian cancer patient populations. Toxicities seen with niraparib include hematologic, gastrointestinal, fatigue, and cardiovascular. Hematologic toxicities include thrombocytopenia, anemia, neutropenia and leukopenia; upfront dose modification to 200 mg niraparib for patients with baseline weight of ≤77 kg and/or baseline platelets of ≤150,000 K/uL should be considered to avoid significant hematologic toxicity, especially thrombocytopenia, based on recent analyses of the ENGOT-OV16/NOVA study. Cardiovascular toxicities include hypertension, tachycardia, as well as palpitations, and patients should be monitored for hypertension. PARP inhibitors have been associated with low risks of acute myelogenous leukemia (AML) and myelodysplastic syndrome (MDS), and the overall risk of AML and MDS is 0.9% of all patients treated with niraparib. Niraparib testing is ongoing in newly diagnosed ovarian cancer patients as maintenance therapy following completion of platinum-based chemotherapy, in *BRCA*wt cancers as treatment, as well as in combinations with other biologic drugs such as immunotherapy and anti-angiogenic agents.

1. Introduction

1.1. Treatment of epithelial ovarian cancer (EOC)

Epithelial ovarian cancer (EOC) remains the most lethal gynecologic malignancy in the United States with 22,440 women estimated to develop the disease and 14,080 estimated to die of this cancer [1]. Globally, approximately 225,000 new cases of ovarian cancer are diagnosed and 140,000 women die of ovarian cancer worldwide each year [2]. The

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https://doi.org/10.1016/j.ygyno.2018.01.011
0090-8258/

mainstay for treatment of newly diagnosed EOC remains surgical debulking and combination taxane- and platinum-based chemotherapy with or without bevacizumab combined with chemotherapy and as maintenance as is approved in the European Union and under review by the US FDA. Responses to platinum-based chemotherapy are high (>80%) but despite this, the vast majority of women will have a relapse of their cancer following a median PFS of approximately 12 months and require more treatment. Recurrent ovarian cancer is defined based on the progression-free interval from the most recent platinum. Platinum resistance defines patients whose cancer regrew <6 months from their last platinum and platinum sensitivity for patients who have recurrent cancer >6 months from their most recent platinum.

Choice of therapeutics to use as second line therapy and beyond is a complex discussion and decision between patient and physician and is informed by the treatment-free interval from the last platinum, genetic and molecular profile of the patient's tumor, residual toxicity from prior therapy, and size and location of recurrent disease. Knowledge of germline mutation status for genes involved in the DNA damage response pathway such as *BRCA1*, *BRCA2*, *BRIP1*, *RAD51C*, *RAD51D*, *PALB2*, and the HNPCC genes are essential to understanding the genetic risk for the patient's family and making appropriate referrals for familial genetic counseling; offering genetic counseling and testing to patients with epithelial ovarian, fallopian tube or peritoneal cancers regardless of age, histology, or family history is an international standard of care [3–5]. In addition, the presence of a germline or somatic *BRCA1* or *BRCA2* mutations identifies patients who, under current indications, qualify for consideration of treatment with a PARP inhibitor (PARPi) [6]. For patients with platinum sensitive recurrence, the standard of care includes re-treatment with a platinum-based therapy, and clinically accepted doublets include carboplatin/paclitaxel, carboplatin/gemcitabine, and carboplatin/pegylated liposomal doxorubicin; patients could also receive single agent platinum. Clinical trials evaluating these doublets report median progression-free survival (PFS) ranging from 8.4 to 11.3 months [7–10]. Despite initial high response rates of 55.6% in those patients with measurable disease at baseline on GOG protocol 213, the median PFS in the group who received placebo as maintenance as opposed to bevacizumab is relatively short and patients will require additional therapy [9]. It is in this setting where PARP inhibitor maintenance treatment following complete response (CR) or very good partial response (PR) is now indicated. Use of bevacizumab during platinum doublet chemotherapy and then as maintenance improved median PFS from 10.2 to 13.8 months (Hazard ratio [HR] 0.613 95% CI 0.521–0.721; p < .0001) and OS from 37.3 to 42.2 months (HR 0.823 95% CI 0.680–0.995; p-0.0447)-in GOG 213 [9] and PFS improved from 8.4 to 12.4 months (HR 0.451 95% CI 0.351–0.580; p < .0001) in the OCEANS trial [7]. Similarly, use of cediranib with and following platinum/taxane chemotherapy improved PFS from 8.7 to 11.1 months (HR 0.57 95% CI 0.45–0.74; p = .024) [11]. In addition to improved PFS, addition of bevacizumab also improved response rates among the 76% of patients with measurable disease In GOG 213. In the chemotherapy plus bevacizumab group the overall response rate was 78% and complete response rate was 32% as compared to 59% and 18% in the chemotherapy alone group [9]. This fact becomes important when one considers the indication for maintenance PARPi among patients with CR or very good PR.

1.2. PARP inhibitors

1.2.1. Mechanism of action

The initial discovery that PARP inhibitors have enhanced anti-cancer activity in vitro in *BRCA*m cancers led to the initial testing of PARP inhibitors as single agents as treatment in *BRCA*m cancers and their eventual regulatory approval; this strategy has been broadened to also include PARP inhibitors as maintenance therapy post-platinum response in the platinum sensitive setting. PARP inhibitors work based on the concept of synthetic lethality, which refers to the presence of an inherent vulnerability in a cell that is, in and of itself not lethal, but when combined with another genetic event may become lethal. The best example of this exists with the presence of *BRCA*m where loss of the BRCA protein results in deficient homologous recombination (HR) repair. The second genetic event leading to synthetic lethality is accomplished by inhibiting PARP proteins 1, 2 and/or 3, which further inhibits HR via interference with MRN complex recruitment as well as blockade of base excision repair (BER) required for single strand break repair [12]. Besides mutations in *BRCA1* or *2*, mutations and epigenetic changes in genes involved in HR can also lead to HR deficiency (HRD) and render tumors susceptible to PARP inhibitors. In addition to the enzymatic effects of PARP inhibition on PARP function, PARP trapping also contributes to the efficacy of PARPi. Normally, the PARP protein binds to sites of DNA damage, synthesizes pADPr polymers which recruit additional repair proteins and subsequently results in the release of PARP from the DNA. If PARP is inhibited, it cannot make these polymers and so never releases from the DNA and obstructs DNA replication forks resulting in chain termination [12].

1.2.2. Clinical studies of PARP inhibitors

Several phase 2 and 3 studies have led to regulatory approval of PARPi's. Olaparib is currently US FDA approved for use in patients with deleterious germline *BRCA*m who have been treated with ≥3 lines of prior therapy and also as maintenance post-platinum response in the platinum sensitive patient without reference to *BRCA* status nor histology FDA [13]. This latest approval was based on SOLO-2 (NCT01874353) which confirmed the results seen in Study 19 and because Study 19 included *BRCAwt* patients, the indication could be expanded to include both *BRCAm* and *BRCAwt* [14,15]. Rucaparib is currently indicated for patients with deleterious germline or somatic *BRCA*m who have been treated with ≥2 lines of prior therapy [16]. Niraparib is currently indicated in the US and has approval from the European Medicines Agency (EMA) as maintenance post-platinum response in the platinum-sensitive patient regardless of *BRCA* status or histology, similar to the olaparib approval [17]. Olaparib has previously been approved by the EMA as maintenance therapy for *BRCA*m patients who are in PR or CR to platinum containing therapy [18]. The role for PARPi in the maintenance setting is an actively evolving story, and several studies have informed these regulatory approvals.

Study 19, a randomized phase 2 (RPh2) trial of olaparib vs. placebo following a CR or PR to platinum-based therapy in the recurrent setting, demonstrated the potential of PARPi to prolong PFS (11.2 vs. 4.3 months) in *BRCA*m patients [19] [20] with benefit of olaparib also observed in the overall intent to treat population as well. The pivotal RPh3 trial, SOLO-2 confirmed these results with a HR of 0.30; 95% CI 0.22–0.41; p < .001; median PFS 19.1 months vs. 5.5 months [8] and led to a new indication for olaparib tablets.

The PARPi rucaparib was evaluated in the ARIEL 3 phase 3 trial which randomized patients with high grade serous or endometrioid cancers and with CR or PR following platinum based therapy to rucaparib 600 mg po bid vs. placebo and reported statistically significant improvements in PFS among patients with somatic BRCA, loss of heterozygosity and intention to treat [21].

The ENGOT-OV16/NOVA trial showed the effectiveness of niraparib in the maintenance setting [22]. This study evaluated niraparib 300 mg po qd versus placebo among patients with high grade EOC who had a CR or PR following platinum-based chemotherapy for platinum treatment-free interval (TFIp) >6 months recurrent disease. This study resulted in an FDA indication and recent EMA approval for niraparib for the maintenance treatment of patients with recurrent EOC who are in complete or partial response to platinum-based therapy regardless of HRD or *BRCA* mutation status of the tumor [23]. This approval was the first approval for a maintenance therapy in ovarian cancer in the United States and the first approval of a PARPi outside of the presence of germline or somatic *BRCA* mutations, thus expanding patient access to PARPi. Given the expected increase in utilization of

Please cite this article as: K.N. Moore, et al., The poly (ADP ribose) polymerase inhibitor niraparib: Management of toxicities, Gynecol Oncol (2018), https://doi.org/10.1016/j.ygyno.2018.01.011