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PARPi related toxicities: do we need more appropriate instruments to evaluate it?

The development of poly(ADP-ribose) polymerase inhibitors (PARPi) for therapy is a successful application of bench-to-bedside medicine and at present represents a major breakthrough in ovarian cancer care.

Almost half of all ovarian cancers present deficiencies in the homologous recombination (HR) DNA repair pathway and PARP inhibitors are being utilized in the clinic to manage recurrent ovarian cancers that display defects in the HR repair pathway. However, PARP inhibitors have also shown significant clinical benefit in patients without HR deficiencies [1].

Between December 2014 and July 2017, three PARPi (olaparib, rucaparib, and niraparib) were licensed for the treatment of recurrent ovarian cancer and approvals for additional disease indications are anticipated. Olaparib received FDA approval as monotherapy in *BRCA* mutated ovarian cancer who had received at least three previous chemotherapy lines [2] and as maintenance in platinum sensitive, platinum responsive ovarian cancer patients' regardless *BRCA* mutation [3]. EMA approval of Olaparib is limited to the maintenance treatment of *BRCA* mutated, platinum sensitive, recurrent ovarian cancer patients who had responded to platinum-based chemotherapy. FDA approval of rucaparib as monotherapy in *BRCA* mutated patients who had received at least two previous chemotherapy lines was announced

on December 2016 [4]. Recently, EMA approved the drug in the same indication. Niraparib has been approved by FDA and EMA for maintenance therapy of recurrent platinum sensitive ovarian, fallopian tube or primary peritoneal cancer, regardless of *BRCA* status [5].

Several adverse events (AEs) to PARPi have been observed and although there are a number of overlapping class specific toxicities, there are also some marked differences for each of them. Class specific toxicities are grade 3 and 4 anaemia that was reported in 18%–45% of patients and nausea/vomiting and fatigue which impact in more than 70% of patients but are mainly grades 1 and 2. In contrast, grade 3 and 4 thrombocytopenia were notably higher in the niraparib trial (33.8%) compared with Olaparib (1%), and Rucaparib studies (5%) while grade 3 and 4 transaminates elevation was a typical Rucaparib toxicity (11%) [6].

Rare ($\leq$1%) but important class-specific AEs also included myelodysplastic syndrome/acute myeloid leukaemia (MDS/AML) and pneumonitis. The incidence of MDS/AML was similar across all PARPi and seems non-influenced by duration of treatment [6].

Notably observed AEs resulted in dose reduction in 25%–66.5% of cases and dose discontinuation in 9%–11% of cases.

In particular, in NOVA trial the recommended dose of niraparib (300 mg/die) did cause prominent grade 3 and 4 haematological (thrombocytopenia 34%; anaemia 25%; neutropenia 20%) and non-haematological (hypertension 8%, fatigue 8%, nausea 3%) toxicities leading to dose reductions in 66.5% of patients and to permanent treatment discontinuation in 14.7% of cases. 74.1% of patients randomized to niraparib and 22.9% assuming placebo reported grade 3 and 4 toxicities the vast majority of which were haematological [5].

Given that lower doses are associated with substantial improvements in the incidence of treatment-emergent AEs while do not appear to compromise efficacy, approaches that would permit the individualization of optimal doses in patients at higher risk of grade 3 or 4 haematological toxicity have been evaluated.

In their retrospective RADAR analysis on Nova trial, Bereck et al. [7] identified two risk factors able to predict myelosuppression (body weight $<$77 kg and/or basal platelets count $<$150 000/μl) suggesting that, when one or both are present, the starting dose of niraparib should be reduced to 200 mg/day. The incidence of grade 3/4 thrombocytopenia was 35% for patients having at least one risk factor compared with 12% in patients without either risk factor and, as a results of dose interruptions and reductions, average daily dose delivered in the first 2 months was 200 mg. Moreover, progression-free survival in patients who were dose reduced to either 200 or 100 mg was consistent with that of patients who remained at the 300 mg starting dose. The author concluded that, in the presence of one or both risk factors the starting dose of niraparib should be 200 mg/die and if no haematological events occur within the first 2–3 months of treatment, consideration for dose escalation may be entertained with close monitoring of blood counts. This analysis is being submitted to regulatory authorities to support consideration for dose modification.

It is not the first time that a new drug enters the market with a dose which is not the one that will be usually used in the clinical setting: Pegylated Liposomal Doxorubicin was labelled for the treatment of recurrent ovarian cancer at the dose of 50 mg/mq every 28 days, but the elevated incidence of grade 3 and 4 hand food syndrome prompted the clinician to reduce the dose to 40 mg/mq q 28 days without any impact on efficacy [8]. Topotecan received the indication for the treatment of recurrent ovarian cancer at the dose of 1.5 mg/mq days 1–5 q 21, but the unmanageable haematological toxicity forced clinicians to reduce the dose to 1.25 mg/mq for 5 days every 3 weeks or to transform the schedule into a less toxic weekly administration [9].

An important point of discussion, particularly in this setting where three drugs appear similar in efficacy but different in safety, is if the data we have from the three registration trials effectively reflect the burden of toxicity during this treatment. The reporting of toxicity as peak toxicity is adequate for a daily chronic therapy that may last months or years? The authors of the present paper should be complimented for going deeply in the NOVA database to better understand the safety issue. More data should be made available from all the studies particularly showing the duration of side-effects. A grade 2 side-effect could be more heavy for a patient than a peak and transient grade 3 AE. How to report this? Area under the curve could be a tool to better report low grade chronic side-effects?

Also the point of view of the patients should be more clearly investigated; it may help in our clinical decision among the three different drugs.

In fact, accurate monitoring of symptomatic AEs is essential in clinical trials to assess and ensure patient safety, as well as to inform decisions related to treatment and/or continuation of trial participation [10]. Usually in oncological studies the safety findings are reported using standard investigator-reported CTCAE grades. There is empirical evidence that investigators miss up to half of symptomatic AEs [11] and that the collection of this information directly from study participants as patient-reported outcomes (PROs) may improve the reliability and accuracy of symptomatic AEs detection. In fact, regardless of which self-reporting measure was used, the majority of studies that directly compared CTCAE and PRO ratings confirmed a poor to moderate association between clinician and patient-based AEs [12].

In 2005, the Food and Drug Administration published a draft guidance document (finalized in 2009) recommending the use of PROs whenever measuring concepts in clinical trials that are better evaluated from the patient's perspective [13] with a similar statement from the European Medicines Agency [14].

At present PROs are used in clinical trials for measurement of health-related quality of life, physical functioning, and disease-related symptoms [15]. In particular, electronic-based PRO-CTCAE system represents the patient's perception of the treatment related symptoms in terms of frequency, severity, and interference with daily life activities, without any potentially misleading interpretation by the clinician, and may assist in the general understanding of a therapy's safety and tolerability.

Multiple studies have demonstrated that PRO-CTCAE data may provide different results than CTCAE for the same symptoms and, as such, the overall evaluation of toxicity needs to be supported by the clinical interpretation [16, 17]. Nevertheless, a patient's perception of symptoms can provide a better understanding of treatment outcomes from the patient's perspective because PRO data are more systematically assessed and often may investigate about different aspects of the toxicity than what

CTCAE may capture. Moreover, one additional advantage of the electronic PRO data registration over the traditional paper method is represented by the ability to collect data between clinical visits providing potential immediacy of the information. As such, there is growing interest in using PRO-CTCAE assessments in the care setting [18] and recently, a systematic review by Gotay et al. [19], demonstrated that PRO-CTCAE measures significantly correlate with patients survival and provide information above and beyond more conventional clinical assessments.

The need for such an approach is particularly outstanding in the modern oncology because we are entering into a new therapeutic era in which long-term, orally administered target therapies and immunotherapies may cause elongated-standing, low grade AEs that contribute to treatment non-adherence, discontinuations, dose reductions, and, above all, patient distress [20].

Nevertheless several challenges and bags need to be addressed: (i) although multiple translations are in progress, translation and linguistic validation of PRO-CTCAE items in other languages are needed; (ii) personnel and infrastructure are required for the collection of data and potential concerns about workload for clinical research staff need to be considered; (iii) there is limited experience with respect to how optimally analysing and interpreting PRO-CTCAE data and is necessary to identify the most informative way to merge symptomatic toxicity scores in combination with CTCAE grades [21].

In conclusion systematic capture of patient perspective can inform the development of new cancer therapies and should be incorporated in clinical trials in order to better capture toxicities and inform the appropriate dosage and schedule of the new drugs before entering into the market. From the informed patient's perspective, the patient voice has been a key missing element in the current system of drug safety assessment and the mistake should not be repeated in the future.

Better reporting of safety in the clinical trials with daily oral therapy is mandatory. High grade peak toxicity may not reflect the full toxicity burden of these drugs. Chronic low grade AEs may be even more important for the patients. PARPi are an incredible step forward for our patients. However, we still need to fully learn how to preserve the benefit reducing the impact of toxicities. The RADAR analysis adds an important information, but more data are needed for all PARPi.

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Identifying patients who may benefit from oxaliplatin-containing perioperative chemo(radio)therapy for rectal cancer

Advances in each of the components of multimodality treatment of rectal cancer—surgery, radiation, and chemotherapy—have significantly improved patient outcomes over the past two decades. Patients are less likely to recur locally and more likely to maintain sphincter function and have a reasonably good quality of life, although the risks of distant recurrence remain substantial. In the era before preoperative chemoradiation and total mesorectal excision, postoperative 5-fluorouracil was associated with an improvement in overall survival (OS) in patients with Dukes' B and C rectal cancer [1]. While neo-adjuvant (chemo)radiation is now considered standard of care, adjuvant (postoperative) chemotherapy has been generally accepted as a component of multimodality therapy for locally advanced rectal cancer with the aim of reducing distant metastases [2, 3]. This acceptance is founded mostly on the basis of extrapolation from adjuvant colon cancer trials and meta-analyses in rectal cancer [4]—despite the lack of any individual trial phase III evidence for benefit in disease-related outcomes. Recently, this strategy has moved chemotherapy earlier up-front based on clinical and pathological response outcomes. Many now endorse a 'total neoadjuvant therapy' (TNT) approach, in which all planned RT and chemotherapy are delivered in the preoperative setting.

The CAO/ARO/AIO-04 phase III trial [5] is one of a series of randomized trials, which investigated the addition of oxaliplatin to neoadjuvant CRT [6–10]. The results showed a small but significant 3-year disease-free survival (DFS) benefit of adding oxaliplatin to 5-FU-based perioperative CRT [5]. This post hoc subset analysis of the effect of age in the CAO/ARO/AIO-04 phase III trial [11], reported in the current issue of *Annals of Oncology*, concluded 'The addition of oxaliplatin significantly improved DFS and OS in younger patients aged <60 years with advanced rectal cancer. Patients aged ≥70 years had no benefit'.

At first sight, this conclusion seems entirely credible and would be in line with a number of publications in colon cancer trials using fluoropyrimidines alone [12] or with the addition of oxaliplatin [13, 14] as well as a combined analysis from the Adjuvant Colon Cancer End Points (ACCENT) database [15]. These publications consistently suggest that oxaliplatin does not have the same efficacy in patients over 70 as it does in younger ones.

Human aging is characterized by both physical and physiological frailty, and an increased susceptibility to infection and cancer. There is a loss of adaptive immunity—specifically with impairment of function and altered distribution of T cells [16], and dendritic cells activation and migration [17]. From the age of ∼60 years, this decline progressively leads to a state of immuno-senescence, which is considered the main cause of diminished vaccine efficacy in older adults. Better outcomes in advanced CRC patients have been reported for oxaliplatin chemotherapy or chemo-immunotherapy if the primary tumour showed marked T-regulatory cell (Treg) infiltration [18]. Oxaliplatin and irradiation induce a similar form of immunogenic cell death [19]. Hence it is not fanciful to imagine that adjuvant chemotherapy drugs such as oxaliplatin with additional immune effects [20] may not be so effective in older adults.

However, a number of issues need to be addressed before accepting the CAO/ARO/AIO-04 present conclusions. Firstly, in a post hoc analysis the hypothesis being tested does not have to be specified before the examination of data. This omission can potentially give rise to substantial limitations if used to try and answer comparative questions of efficacy. Patients are not randomized, and sources of bias are therefore not controlled for.

Secondly, the inherent design of the trial does not allow us to distinguish if any benefit in DFS from the addition of oxaliplatin in younger patients <70 years (which is lacking in older patients) derives from the preoperative concurrent CRT component or the use of postoperative oxaliplatin, or both.

Thirdly, it is just possible that the real outlier here is the 240 patients in the control group under 60, who fare badly despite a significantly better performance status ($P = 0.001$) than the older two groups. The results show 3 year DFS (67%) in the under 60 control versus 78% in those who received oxaliplatin $P = 0.011$). In addition, both the local recurrence (7%) as well as metastatic rate (26%) for the under 60s control group is higher than in any of the other groups (see Table 1). Compliance to treatment with both radiotherapy and chemotherapy appear similar.

Demonstrating a benefit from adjuvant chemotherapy in older patients is thought to be harder mostly due to a higher rate of deaths from other causes. This observation is reflected in the DFS and OS figures for the over 70s which are lower numerically than in the younger groups both in the control as well as in the experimental arms.

The potential benefit of adding oxaliplatin to CRT and its use in the adjuvant setting remain controversial. None of the randomized trials conducted so far demonstrated any OS benefit from the addition of oxaliplatin to standard CRT [6–10].

Systematic reviews of randomized trials evaluating the addition of oxaliplatin have also been reported, with different conclusions. Yang et al. [21] conducted a systematic review of all seven trials; the DFS analysis excluded the NSABPR-04 trial and showed an HR ratio of 0.89 (95% CI 0.78–1.00; $P = 0.05$) in favour of oxaliplatin-CRT. This DFS analysis included two of the trials in which adjuvant treatment with oxaliplatin was added in the