Letter to the Editor

Dear Sir,

in their recent paper Prof Ledermann and Dr Luvero addressed the rationale to combine PARP1 inhibitors (PARP1-Is) and anti-angiogenic therapies providing plausible initial evidences in epithelial ovarian cancers (OC). Indeed and despite the fact of exploratory studies in several other cancers, as of today, PARP1-Is have demonstrated clinical efficacy in OC only or, more precisely, in the subset of this tumor group bearing a genetic defect in the homologous recombination (HR) repair of DNA damage. As single agent PARP1-Is have been studied in other tumors bearing HR-deficiency as pancreatic, prostate and breast cancers [1, 2]. Since PARP1-Is have been proven difficult to be used with other antitumor compounds, the combination with anti-angiogenic therapies is certainly a worth to explore hypothesis: toxicity should not be superimposable and targeting angiogenesis is the other recent significant improvement in OC treatment [3, 4].

For long time the use of anti-angiogenic therapeutics was debatable due to their induction of hypoxic conditions that made tumor cells more aggressive and prone to metastatization. Nonetheless, hypoxia increases the DNA damage and soften the DNA repair machinery generating a peculiar sort of BRCAness [5]. In this context, hypoxia might be turned to the light side being potentially mechanistically involved in the mutual enhancement and synergistic effect of PARP1-Is and antiangiogenic agents. On the other hand, the emerging concept of anti-angiogenic-induced vasculature normalization robustly sustained by growing body of evidence [6, 7] redirects the benefit obtained by anti-angiogenic strategies towards the amelioration of hypoxic condition and a reduction of aggressive tumor phenotypes. In this context the potential synergism of anti-angiogenic agents and PARP1-Is might originate from the increased availability of PARP1-Is that reach tumor cells and the reduction of aggressive and drug resistant inducing conditions, especially in HR-defective cells.

Regardless the undoubtedly great interest of this future development, it is a pity that clinical researchers have not yet found a strategy to use PARP1-Is in combination with cytotoxics as well. Indeed, presently, PARP1-I usage pursues so called synthetic lethality in HR-defective tumors only [8]. Unfortunately, we have not yet found a way to exploit the whole potentiality of PARP1-Is as chemopotentiators to sensitize DNA-damage induced by other therapies. Thus, this inhibitor class seems greatly underexploited so far. For instance, Ewing's sarcoma displayed the greatest sensitivity among a comprehensive set of tumor cell lines, but this exquisite opportunity did not have any clinical application so far [9, 10]. Indeed, aside from BRCA-deficient OC, the only other large experience is represented by the trial in prostate cancer [2].

Considering the mechanisms of action of platinum and data emerged from studies in OC wherein both platinum and PARP1-I sensitivity were correlated with defects in homologous recombination DNA repair [11], it is reasonable to hypothesize that in other cancers with DNA-repair defects this combination might be active as well [2]. Other trials exploring various combination

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between PARP1-Is and cytotoxics have been unsatisfactory: temozolomide in Ewing' sarcoma and melanoma; liposomal doxorubicin in OC and other tumors; gemcitabine in pancreatic cancer [12]; topotecan in uterine cervical cancer [13]. Hematological dose-limiting toxicities were observed in a proportion greater than 50% of the patients making it a clinical significant constraint. Of course, ionizing radiations also induce a DNA-damage that elicits PARP1 activity and therefore, its inhibition could also be rationally exploited to make tumor DNA-damage irreparable. Once again, the extent of radiosensitization greatly depends on the olaparib dose, radiation dose and homologous recombination status of cells [14].

Hence, several unanswered questions prevent PARP1-Is to become a true protagonist in cancer treatment. First, we need a better understanding on how to handle PARP1-Is in the clinical setting beyond HR-deficient tumors. Second, we have to learn how to modulate their dosage and schedule so as to reduce hematological toxicity and make combinations with both chemotherapy and radiotherapy sustainable. Third, timing with chemotherapy is far from understood and PARP1 expression is modulated by chemotherapy itself [15]. Finally, despite the fact that DNA-damage repair pathways are redundant, the selective inhibition of a key enzyme as PARP1 should affect tumor cell ability to repair DNA-damage independent of BRCA1/2 mutations or so called BRACness. Thus, PARP1-Is are expected to have at least some activity in HR proficient tumors as well. The comprehension of how to take advantage of PARP1-Is in a larger proportion of patients is crucial to bring this innovative therapy to the largest number of patients.

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