


# Combinatorial Therapy of High Dose Vitamin C and PARP Inhibitors in DNA Repair Deficiency: A Series of 8 Patients

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## Abstract

**Background:** Tumor-specific DNA repair defects are ubiquitous in cancerous tissue, which offers a potential for clinical gain to build on these perturbations. Intravenous high-dose vitamin C (IVC) triggers the formation of hydrogen peroxide ( $H_2O_2$ ), which contributes to Fenton chemistry producing hydroxyl radicals ( $-OH$ ), causing selective damage to DNA. Herein, we evaluated the therapeutic response to IVC and PARP inhibitors (PARPi) in combination in 8 patients with a deficiency of homologous recombination repair system (dHRR) in a 3-year period.

**Material and Methods:** Eight patients with progressive stage IV malignancy, who were pre-treated with conventional methods, were admitted to our clinic. Subsequent therapy has included IVC at a dose that was set to be in the range of 1 to 1.5 g/kg, although 1.25 g/kg was dominantly administered. Furthermore, following genomic evaluation, PARPi (niraparib or olaparib or talazoparib) was chosen to be used in combination with IVC which was administered 2 to 4 times a week.

**Results:** In the present study, we achieved partial response in 5 patients and complete response in 3 patients. Grade 2 anemia and fatigue toxicities were observed in some cases, while grade 3 toxicity was not found in any of the patients.

**Conclusion:** Our 8 patient case study shows that IVC could be a plausible additional therapy for HRR deficiency. Although the single agent PARPi therapy is effective for metastatic disease, an overall survival (OS) advantage has not been demonstrated. Our results suggest that adding IVC can improve PARPi therapy outcomes. To fully endorse the results stated above, combinatorial therapy of intravenous high dose vitamin C and PARP inhibitors needs to be reviewed in broader cohorts of patients.

## Keywords

PARP inhibitors, vitamin C, ascorbic acid, high dose vitamin C, cancer, deficiency homologous recombination repair system, DNA repair deficiency

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## Introduction

Vitamin C (Vit C) has been screened as a possible anti-cancer agent, which acts effectively either as monotherapy or in conjunction with conventional chemotherapies.<sup>1</sup> Supporting evidence from a plethora of burgeoning preclinical and clinical studies have led to a renewed interest in the clinical effectiveness of IVC as a cancer chemotherapeutic agent. Its administration creates a synergy with chemotherapy and reduces side effects triggered by chemotherapeutic regimens.<sup>2</sup> The cytotoxic action conferred by IVC is mostly caused by two distinct mechanisms. Firstly, IVC causes hydrogen peroxide ( $H_2O_2$ ) generation that in turn reacts with the increased labile iron pool (LIP) in cancer cells to mediate Fenton chemistry and cause damage to cellular

macromolecules via oxidative processes.<sup>3,4</sup>  $H_2O_2$ , which is a form of reactive oxygen species (ROS), can pass through the cell membrane, and it is produced extracellularly and/or intracellularly in the presence of pharmacological ascorbate.<sup>3,4</sup> Moreover,  $H_2O_2$  has several downstream targets and these targets, when effected, primarily cause DNA damage, mitochondrial damage, and apoptotic pathway activation. Secondly, IVC-related excessive oxidation leads to the

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generation of an unstable metabolite, dehydroascorbic acid, which portrays cytotoxic activity.<sup>5</sup>

IVC show a selective cytotoxicity against cancer cells. This pattern has been addressed by preclinical data on 2 selective cytotoxicity mechanisms. First, high dose ascorbate is shown to provide increased and steady-state  $H_2O_2$  level and increased LIP in cancer cell which eventually causes consistent redox cycling.<sup>4,6,7</sup> Subsequently, this redox cycling causes DNA and macromolecular damage. Additionally, increased LIP is a feature of cancer cell. Furthermore, cancer cells show altered iron metabolism (increased expression of transferrin receptor 1 and hepcidin and low levels of ferroportin), which leads to increased LIP.<sup>7</sup> Secondly, tumor cells have a decreased ability to metabolize  $H_2O_2$  due to low antioxidant enzymes level (eg, catalase, glutathione peroxidase).<sup>6,8,9</sup> As a result, high dose ascorbate toxicity is closely related with increased LIP and decreased capacity of metabolizing  $H_2O_2$ . Moreover, catalase or iron chelating agent addition to cell culture media inhibit the IVC toxicity.<sup>4</sup>

Due to increased metabolic turnover, which is related to oxidative and inflammatory manifestations of the pathophysiology of cancer, patients with tumor burden often face an impaired status of Vit C.<sup>10</sup> Furthermore, a persistent rise in oxidative stress and the levels of pro-inflammatory biomarkers in the biological microenvironment are the noted after-effects of chemotherapeutic regimen.<sup>6</sup> Conclusively, patients with cancer often have an elevated requirement for Vit C. It is also reported that animals with the ability to self-synthesize Vit C display increased levels of Vit C when subjected to high tumor burden, thereby suggesting its increased necessity.<sup>11</sup>

Additionally, poly (ADP-ribose) polymerase inhibitors (PARPi) are categorized as a new anti-cancer therapy that have gained considerable interest in recent years.<sup>12</sup> By triggering an abnormality in the DNA repair mechanism, they ideally function by the mode of synthetic lethality, leading to death in cancerous cells. The projection of the PARPi mechanism is rather complex, and implies 2 distinct ways of inducing cytotoxicity. First, PARPi inhibit enzymatic activity resulting in subsequent DNA repair errors which in turn lead to cell death. Second, the caging of PARP1, whereby preventing autoPARylation and freeing PARP1 from the damaged DNA eventually contributes to cell death in repair-deficient cells.<sup>13,14</sup>

Chemotherapy is still accepted as the backbone of several cancer therapies. Nevertheless, chemotherapy responses are interventions that are restricted by either de novo or acquired resistance and therefore, combination therapies that improve chemotherapy responses are eagerly sought. Inhibiting DNA repair has long been suggested to boost genotoxic treatment as a rational and reasonable sensitization method.<sup>15</sup> Still, it is essential for researchers to ask themselves whether chemotherapy plus PARPi in combination is a double-barreled gun

or a dangerous weapon. It should be considered that numerous data have indicated that the combination of PARPi plus chemotherapy at the commonly used dose often induces toxicity to normal tissues and this side effect is also accompanied with trapped PARP1 inhibitors.<sup>16</sup> Therefore, we need selective DNA damaging agents to improve PARPi effectiveness. This study has shown us that IVC might be an appropriate choice for it.

Herein, we evaluated the therapeutic response in 8 patients who were administered a combination of IVC and PARPi during a 3-year period.

## Material and Methods

Eight patients with progressive stage IV malignancy presented to our clinic. All the patients had been pre-treated with conventional methods. All patients were reassessed with CT and/or PET/CT before treatment, and PARPi plus IVC treatment was initiated after progression was detected. Genomic evaluation for designing personalized therapy was recommended to those patients. A defective homologous recombination repair (HRR) mechanism was observed in the 8 patients with a FoundationOne CDx test and targeted Next Generation Sequencing (NGS) panel. All patients were informed about the genomic profiling procedure and the rationale regarding IVC therapy and PARPi. This structured evaluation of 8 patients was granted an ethical approval by Mediana Ethical Board (No:016/2020). Written informed consents were obtained from each patient before initiation of therapy involving IVC and PARPi, and consent forms for publication were signed by patient and medical oncologist.

### High-Dose Intravenous Vit C (IVC) Therapy

The dose of Vit C was determined according to the standard Riordan IVC protocol.<sup>17</sup> The initial dose of IVC was set at 15 g to assess the tolerance of the patient, and blood samples were collected simultaneously to assess the activity levels of glucose-6-phosphate dehydrogenase (G6PD). Following confirmation of normal G6PD activity levels in patients, the target dose was determined to be in the range of 1 to 1.5 g/kg. Dose elevation was titrated up to a therapeutic range of 50 to 100 g per infusion and IVC was administered 2 to 4 times a week. Except for patient 1 (anaplastic prostatic adenocarcinoma), all patients' IVC treatment were administered in our clinic. Patient 1 lives in Azerbaijan; he presented to our clinic and his diagnosis and treatment plan was made there. Although, Patient 1's initial 1-month treatment of IVC plus PARPi was administered in our clinic, his treatment has continued in Azerbaijan under our supervision, and the patient's laboratory and imaging reports were regularly sent to our clinic. Hence, although we have all the reports of that patient, we could not obtain patient images.

**Table 1.** Baseline Characteristics of the Patients.

Patient	Sex, age	Tumor type	Prior therapy	Metastasis region	Genomic alteration
1	M, 77	Prostate anaplastic carcinoma	HT, RT, chemo	Peritoneal carcinomatosis, LN	BRCA2 loss
2	M, 80	Prostate small cell carcinoma	2 lines chemo	LN, lung, bone	BRCA1 E149*
3	F, 39	Breast cancer	3 lines HT, 2 lines chemo	Liver	BRCA2 T3033fs*11
4	M, 44	Pancreatic neuroendocrine tumor (pNET)	Liver metastasectomy, 2 lines chemo, 3 times liver radioembolization	Liver	BRCA2 R2842C
5	F, 52	Gastric cancer	FOLFOX	Liver, LN	PALB2 N186fs*4
6	F, 56	Ovarian cancer	2 lines chemo (paclitaxel + carboplatin, gemcitabine + cisplatin + bevacizumab) platin- refractory	Peritoneal carcinomatosis	BRCA1 c.690delG
7	M, 63	Pancreatic cancer	2 lines chemo (gemcitabine + capacitabine; FOLFOX)	Pleura and lung metastases	ATM T554M
8	F, 57	Ovarian cancer	3 lines chemo platin- refractory	Peritoneal carcinomatosis	BRCA1 P871fs*31, K711_T900del

Abbreviations: HT, hormonal therapy; RT, radiotherapy; LN, lymph node; FOLFOXIRI, folinic acid, 5-fluorouracil, oxaliplatin.

### Defective HRR and PARPi Therapy

Defective HRR was illustrated in addition to BRCA mutations and RAD51, RAD54, RPA1, NBS1, ATR, ATM, DSS1, CHK1, CHK2, FANCA, and FANCC deficiencies. Impairment in the repair of DNA damage by homologous recombination and sensitivity to PARP inhibition was noted.<sup>18</sup>

The patients were treated with either niraparib at a dose of 300 mg/day, olaparib at a dose of 300 mg/bid or talazoparib at a dose of 1 mg/day. Dose adjustments were performed according to the observed side effects in the treated patients. At the beginning of the treatment schedule, 5 patients were treated with either niraparib or olaparib (supplied from other countries since PARPi was not available in Turkey). Subsequently, Turkish Ministry of Health has approved the Talazoparib Compassionate program for 4 of our PARPi treated patients. Therefore, niraparib or olaparib treated patients were switched to talazoparib therapy. Out of the 8 patients, treatments of 3 patients were initiated with the Talazoparib Compassionate Program.

All patients had Eastern Cooperative Oncology Group performance status of either grade 0, 1, or 2; and adequate bone marrow, hepatic, and renal function along with the standard level of G6PD. Hematology, clinical chemistry, vital signs, and physical examinations were also performed prior to the start of the treatment regimen. Details of the pre-treatment regimen were also recorded.

### Results

A total of 8 patients were evaluated in a 3-year period. Baseline characteristics of each patient are elaborated in Table 1. A combined therapy involving IVC plus PARPi

was administered to the patients and details of the treatments and outcomes are illustrated in Table 2. Figures 1 to 7 depict the pre- and post-treatment PET/CT scan images of the patients (patients 2-8). All the patients were stage IV and pretreated with suitable conventional therapies (radiotherapy, hormonal therapy, chemotherapy, radionuclide embolization). As a result, good response and tolerability were observed with IVC plus PARPi. During the treatment schedule, the dose of olaparib was reduced in 1 patient owing to an observed state of fatigue (grade 2-3), while dose reduction for niraparib was not needed. Only grade 1-2 nausea and anemia remained following the dose reduction, signaling good PARPi tolerability.

The most common side effects observed in the patients were noted to be grade 1 anemia, fatigue, dry mouth, headache, and asthenia. Additionally, elevation of serum creatinine level was observed in 1 patient treated with olaparib and IVC while the normal renal function was resumed after the change of therapy to talazoparib and IVC. The observed effect indicated the possibility that olaparib at the stated dose led to the rise in serum creatinine level. The toxicity profiles encountered by the patients during the study are presented in Table 3. The side effects encountered were thought to be related to PARPi.

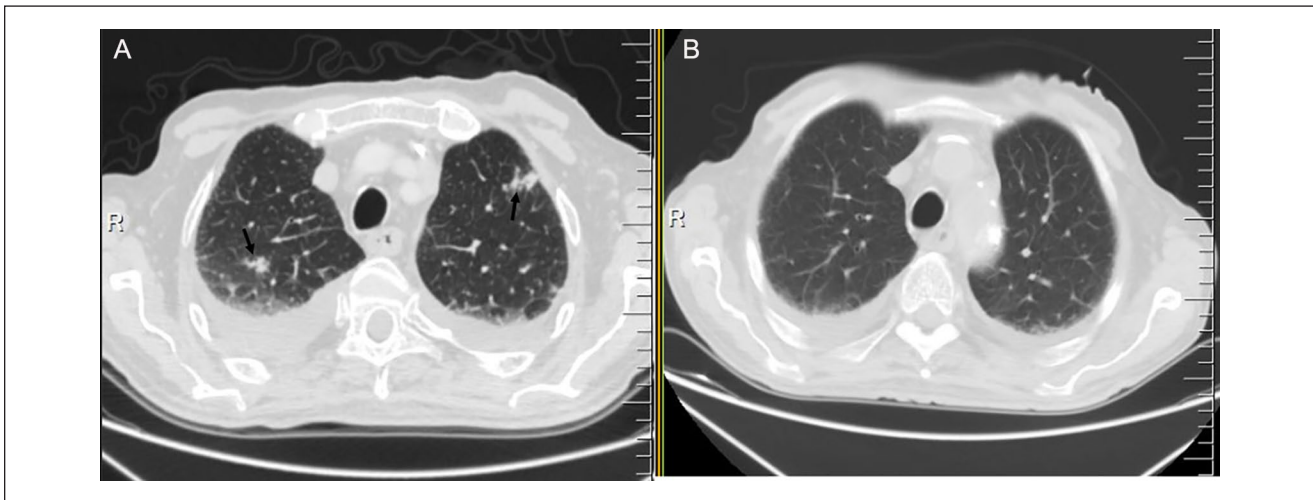
We achieved reasonable response rate and good tolerability with IVC plus PARPi combination. Furthermore, 3 complete and 5 partial responses were observed throughout the therapies. IVC treatments of all patients were performed regularly for the first 3 months, although treatment frequencies were reduced subsequently (mostly 2 times a week). Although IVC treatment was never stopped, its frequency was reduced up to 1 time per month in 3 patients who have showed complete response. In patients with partial response,

**Table 2.** Summary of the Therapies and Outcome.

Patient	Tumor type	PARPi	IVC	Response	TTP (months)	OS (months)
1	Prostate anaplastic carcinoma	Niraparib + Olaparib	1-1.2gr/kg 2-3 times weekly	CR	41+	41+
2	Prostate small cell carcinoma	Niraparib + Talazoparib	1-1.2gr/kg 2-3 times weekly	PR	18	27
3	Breast Cancer	Olaparib + Talazoparib	1-1.2gr/kg 4 times weekly	CR	16	20+
4	Pancreatic neuroendocrine tumor (pNET)	Olaparib + Talazoparib	1-1.2gr/kg 2-3 times weekly	PR	15+	15+
5	Gastric Cancer	Olaparib + Talazoparib	1-1.2gr/kg 2-3 times weekly	PR	12	16
6	Ovarian cancer	Talazoparib	1-1.2gr/kg 2-3 times weekly	PR	8	10
7	Pancreatic cancer	Talazoparib	1-1.2gr/kg 2-3 times weekly	PR	12	18+
8	Ovarian cancer	Talazoparib	1-1.2gr/kg 2-3 times weekly	CR	12+	12+

The survival of patients (in months) who were still alive at the time of completion (and submission) of this study were designated with a "+" symbol after the completion of the number of actual months.

Abbreviations: CR, complete response; PR, Partial response; ECOG, Eastern Cooperative Oncology Group; HT, hormonal therapy; RT, radiotherapy; LN, lymph node; Vit C, vitamin C; PARPi, poly ADP ribose polymerase inhibitor; IVC, Intravenous Vit C; OS, overall survival; FOLFOXIRI, folinic acid, 5-fluorouracil, oxaliplatin, and irinotecan; TTP, time to progression.



**Figure 1.** Metastatic lesions in the patient with prostate cancer (patient – 2). (A) Pre-treatment—Presence of bilateral metastatic nodules (black arrows) in the upper lobes of lungs in the patient with small cell prostate carcinoma. (B) Post-treatment—Near complete response was achieved.

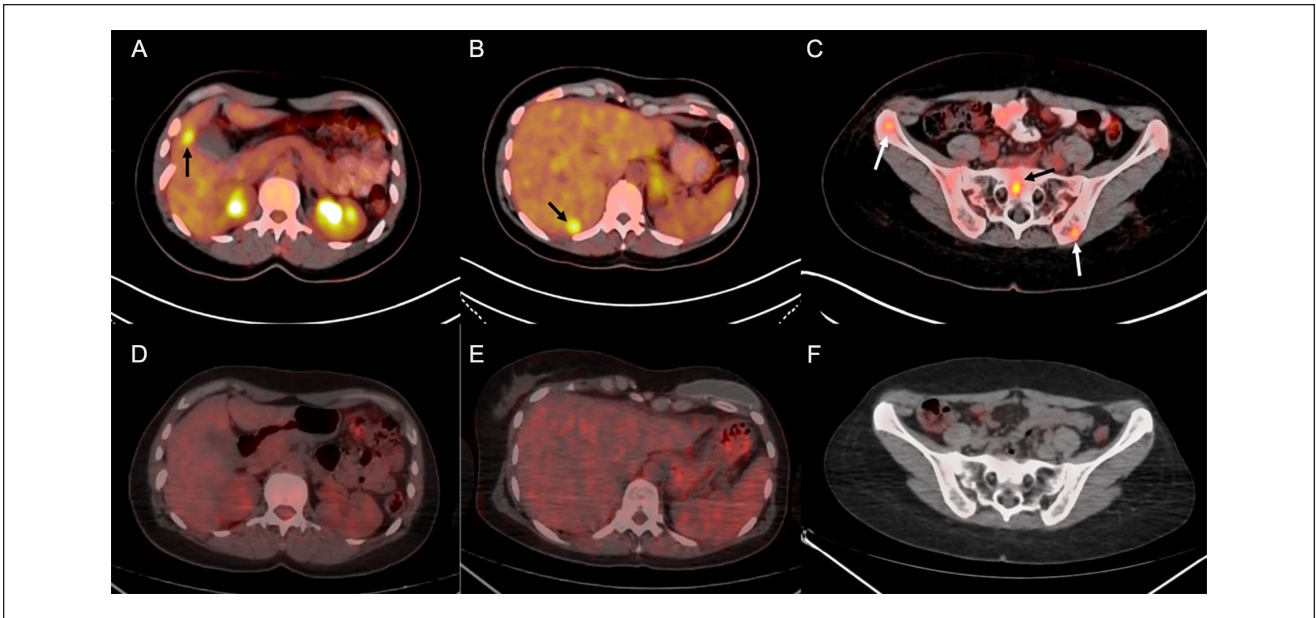
the frequency of IVC treatment was reduced after 6 months and IVC was mostly administered 2 consecutive days every 2 weeks.

## Discussion

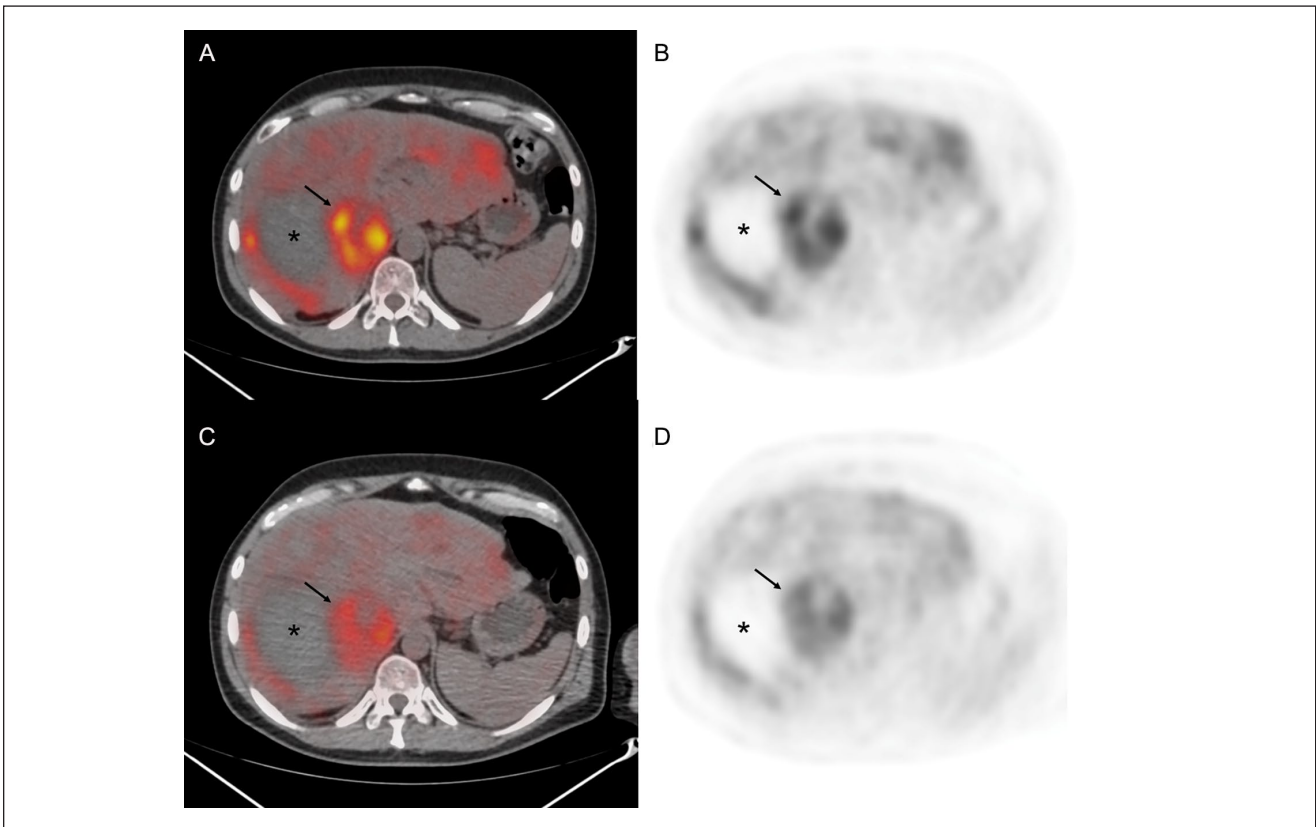
Personalized medicine aims to employ tailored treatments with greater selectivity and efficiency in pre-selected patient populations. One potential pharmacologically targeted treatment

model is set by using small molecule PARP inhibitors in tumors which harbor a deficiency in the homologous DNA recombination pathway, notably due to BRCA mutations. Clinical studies involving several PARPi are currently being undertaken to establish the toxicity, effectiveness, and significance of medications as mono-therapies or in conjunction with radiotherapy or other chemotherapeutic agents in gynecological malignancies and other types of solid tumors, including head and neck, rectal, kidney, pancreas, heart, squamous cell



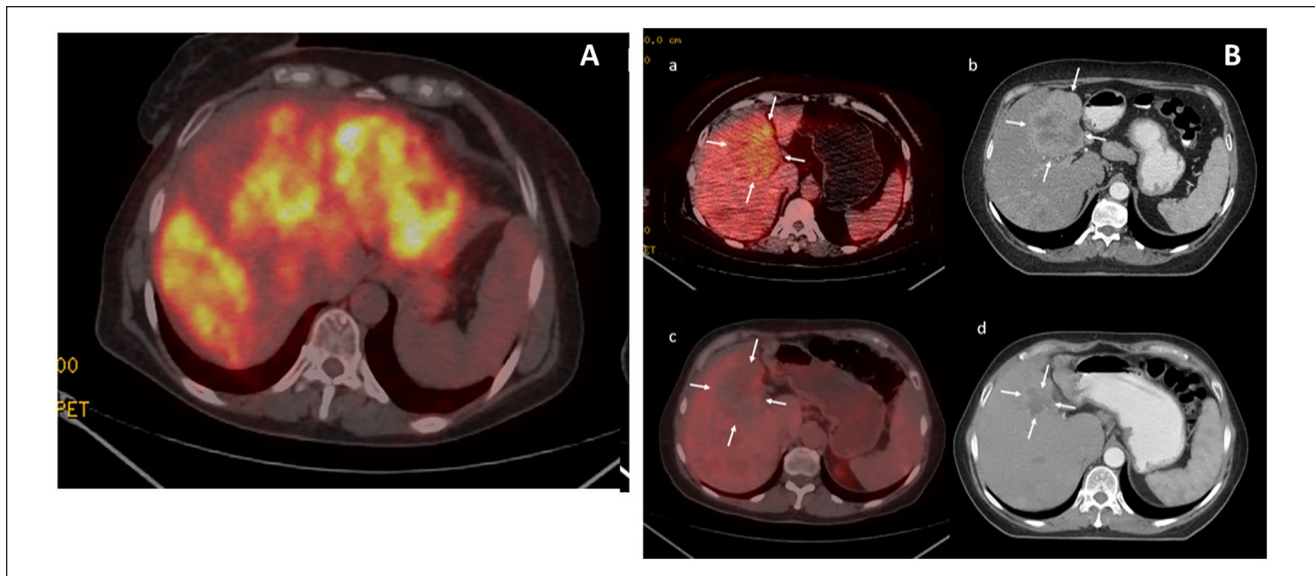


**Figure 2.** Metastatic lesions in the patient with breast cancer (patient – 3). The upper row shows pre-treatment liver (A, B) and bone (C) metastasis (black and white arrows). The 6 months IVC plus PARPi post-treatment PET/CT scan indicates complete response both in liver (D, E) and bones (F).



**Figure 3.** Metastatic lesions in the patient with pancreatic neuroendocrine tumor (patient – 4). (A, B) Hypermetabolic metastatic lesion in the right lobe of the liver (black arrow) in the patient, pre-treatment. (C, D) Images of depicting partial response in the same patient, 8 months post-treatment.

\*Previous liver metastasectomy defect.



**Figure 4.** Metastatic lesions in the patient with gastric carcinoma with diffuse hypermetabolic liver metastasis (patient – 5). (A) Initial PET/CT scan in patient-5 with gastric carcinoma with diffuse hypermetabolic liver metastasis. FOLFOX chemotherapy with high dose vitamin C was administered as first-line therapy\* (B) (a, b) After FOLFOX chemotherapy, PET/CT scan and CT scan (b) shows liver metastasis (segment IV) extending to the right lobe (white arrows). (c, d) After PARP plus IVC, follow-up CT scan (d) shows morphologic marked partial response but consequent PET/CT scan (c) right after CT shows metabolic complete response.

\*Treatment was discontinued due to the chemotherapy side effects and biopsy was performed again from liver metastases (4-2a) and then IVC plus PARPi was started.

carcinomas, and other sarcomas. A substantial research endeavor has demonstrated the pertinence of PARPi usage as chemo-potentiators or chemo- and radiosensitizers in cancer care beyond BRCA mutations.<sup>19</sup>

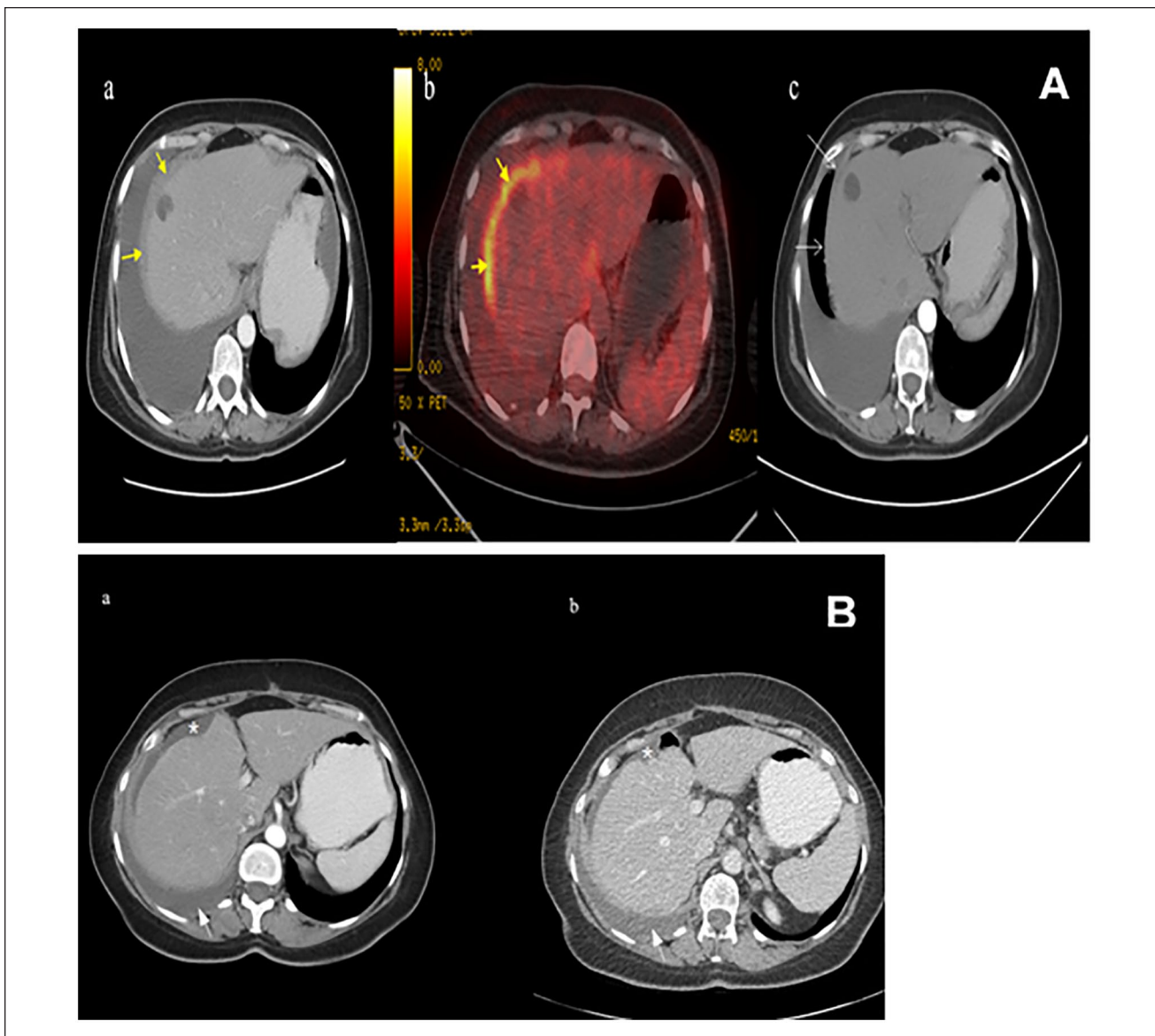
At this stage, combinatorial therapy of PARPi with chemotherapeutics emerges to be a novel strategy with a considerable therapeutic appeal. However, the challenges associated with this therapy limit its potential usage. For instance, a major challenge stands out to be the narrow therapeutic window of combinatorial therapy, since the simultaneous PARP inhibition is not tumor cell-specific. Instead, inhibition of PARP in normal cells abolishes a major DNA repair mechanism in these cells, thus increasing chemotherapy toxicity such as myelosuppression and pharmacological drug-drug interactions. A study in metastatic triple-negative breast cancer involving combinatorial weekly paclitaxel and olaparib reported major myelosuppression.<sup>20</sup> This protocol was consequently evaluated in a phase 3 trial on advanced gastric cancer, and amid promising randomized phase 2 results, olaparib and a weekly dose of paclitaxel showed no improvement in the OS or progression-free survival when compared to paclitaxel administered weekly.<sup>21,22</sup>

Due to the pharmacokinetic properties of the poorly water-soluble oral inhibitors, the prevailing concern with PARPi therapy is the suboptimal availability and retention of the drug at the expected anatomical tumor location. Therefore, optimizing the drug regimen is a crucial factor

for an effective clinical trial with combined treatment approaches.

Preclinical studies revealed DNA damage followed by activation of PARP in cancer cells treated with Vitamin C.<sup>23</sup> In vitro and in vivo trials showed that the combination of IVC plus PARPi (olaparib) was more effective than IVC alone.<sup>24-26</sup> In the preclinical study recently reported by Ma and colleagues, which claims the higher effectiveness of the combination of IVC plus PARPi when compared to their sole usage, they interestingly showed that IVC can also down-regulate BRCA1, BRCA2 and RAD51 expressions. In other words, IVC seems to create a “BRCAness phenotype” and that phenotypic effect may additionally potentiate PARPi effectiveness. Hence, these reported data suggest that the combination of IVC plus PARPi may be effective in both dHRR and intact HRR.<sup>26</sup> Carr and colleagues have published suggestive evidence that IVC can increase the quality of life in cancer patients and minimize various facets of fatigue.<sup>27</sup> While in BRCA-mutant patients, PARPi can elicit significant and sustained anti-tumor responses, still in some instances, resistance to PARPi might emerge as well.<sup>28</sup> IVC related selective DNA damage and epigenetic reprogramming may inhibit resistance to PARPi. Recently, IVC was shown to activate the TET2 activity and accorded sensitivity to the inhibition of PARP.<sup>29,30</sup>

Single agent PARPi therapies also showed good response rate and superior survival data compared with standard chemotherapy (OlympiAD and EMBRACA trial).<sup>31,32</sup> In the



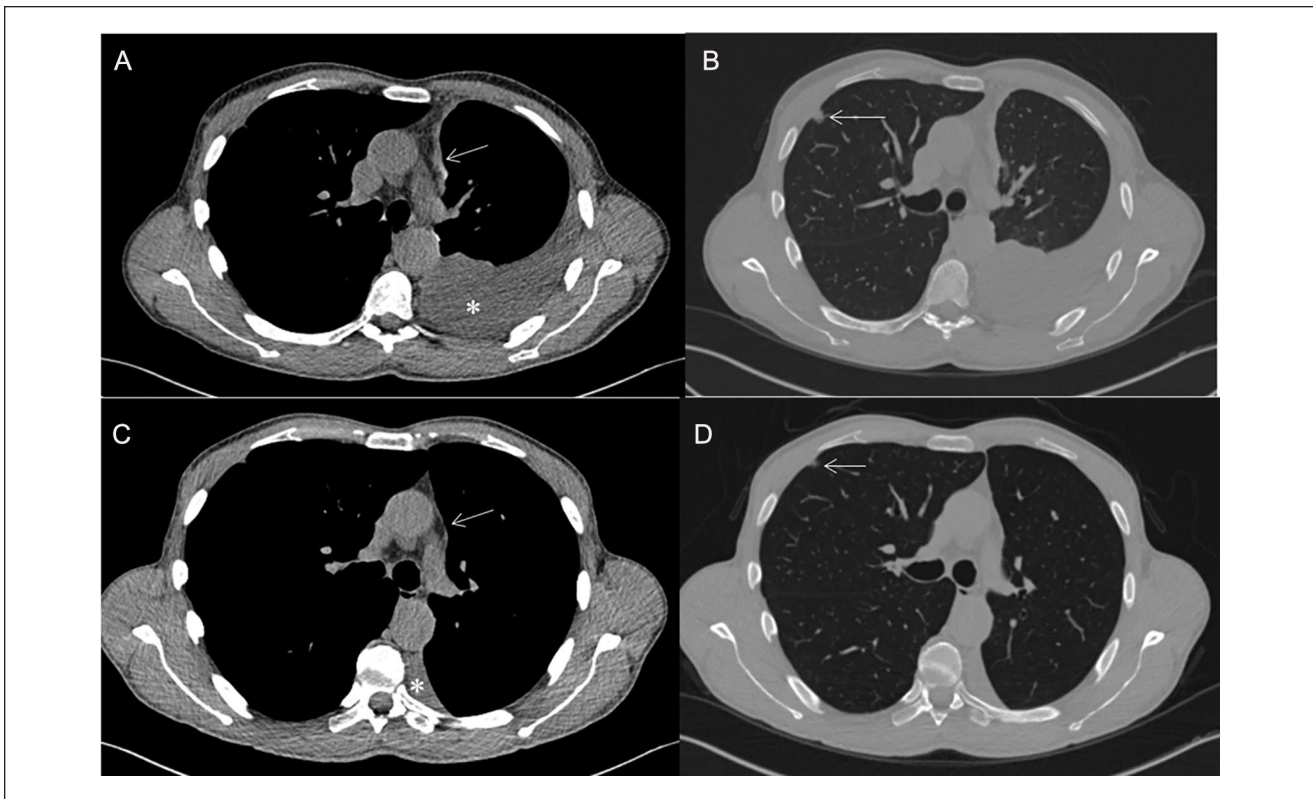
**Figure 5.** Metastatic lesions in the patient with ovarian cancer (patient-6). CT scan and fusion image of PET/CT scan. (A) (a, b) Tumor implants adjacent to the hepatic capsule (yellow arrows) (c) Complete response of capsular implants of the liver (white arrows) (B) (a, b) A 6-month follow-up CT scan after partial response in a patient with peritoneal involvement. Stable disease was noted without tumor implants in the peritoneal surface. Ascites (\*) and right pleural effusion (arrow) were also stable.

OlympiAD trial, the partial response rate was found to be 59.9%, 9% of which was determined to be complete response. Moreover, in the EMBRACA trial, response rate was seen 62.6% with 5.5% complete response. Both of the trials showed statistically significant improvement in progression-free survival, but no differences were found in OS. Poggio et al. have evaluated single-agent PARPi effectiveness against BRCA-mutated HER-2 negative metastatic breast carcinoma.<sup>33</sup> This meta-analysis showed that, considering only measurable disease, the objective response rate in the PARPi group was 61.4% and chemotherapy group

27.8% (OlympiAD and EMBRACA trial; OR 4.15 (95% CI 2.82-6.10,  $P < .001$ ). On the other hand, that meta-analysis did not show any significant difference in OS between two groups (19.6 vs 19.5 months).

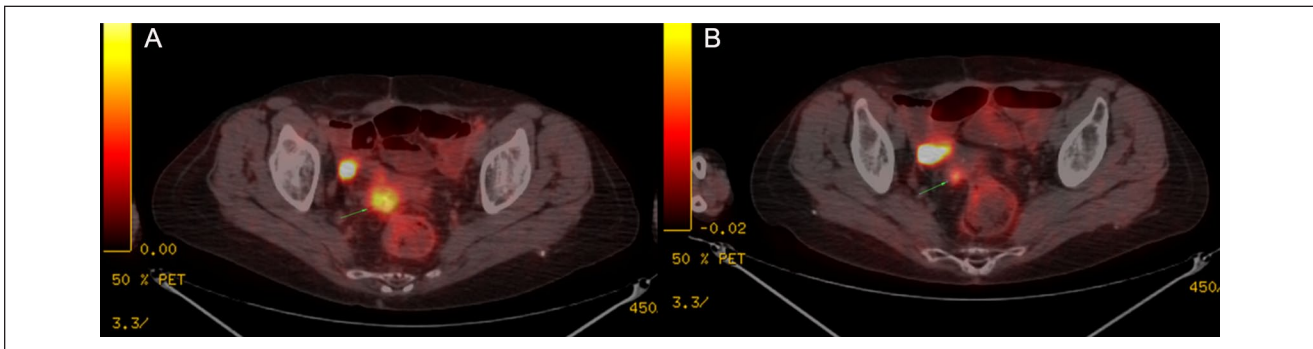
The treatment scheme of the combination of PARPi and IVC in both dHRR and non-HRD cases remains a puzzle. Our experience suggests that IVC treatment may be administered more frequently at the beginning (3-4 times a week) and then reduced according to the response status. We also suggest that after lengthy treatment with IVC given 3 consecutive days a week, patients' adherence to the regimen





**Figure 6.** Metastatic lesions in the patient with pancreatic cancer (patient – 7). (A, B) mediastinal pleural involvement and metastatic pulmonary nodule in the right upper lobe as detected in a follow-up CT scan (arrows). (C, D) After treatment, there was no pleural involvement and nodules were diminished in size (arrows).

\*Pleural effusion was decreased in size.



**Figure 7.** Metastatic lesions in the patient with ovarian carcinoma (patient – 8). (A) Depicts the carcinoma pre-treatment. (B) Partial response was achieved 6 months post-treatment.

tends to decline. Therefore, we think initial response may be important in PARPi plus IVC administration for therapy compliance. If good early response is achieved, long-term adherence can be improved by decreasing the frequency of IVC treatment, and in fact, we observed better adherence in patients for whom the frequency of IVC treatment was reduced after the 3rd month. On the other hand, there was no notable treatment compliance problem for PARPi usage.

Although, it is not possible to determine the IVC + PARPi combination scheme with this limited data, the selective DNA damage provided by IVC can be evaluated to be important at the beginning of the treatment and this process may be continued with single agent PARPi, depending on the response status. Therewith, additional effects of IVC, such as BRCA1, BRCA2 and RAD51 suppressions, will have an effect on determining the treatment scheme with



**Table 3.** Toxicity Profiles of the Patients.

Number of patients			
Toxicity	Grade 1	Grade 2	Grade 3
Anemia	5	3	-
Blood and lymphatic system disorders—other	-	-	-
Fatigue	5	3	-
Fever	-	-	-
Non-cardiac chest pain	-	-	-
Constipation	3	-	-
Diarrrhea	2	-	-
Dry mouth	8 (during IVC infusion)	-	-
Nausea	2	1	-
Stomach pain	2	-	-
Vomiting	-	-	-
Gastrointestinal disorders	-	-	-
Urinary tract infection	1	-	-
Lymphopenia	2	-	-
Thrombocytopenia	-	-	-
Generalized muscle weakness	4	-	-
Dysgeusia	3	-	-
Headache	5 (during IVC infusion)	-	-
Cough	-	-	-
Flushing	-	-	-
Hot flush	-	-	-
Respiratory, mediastinal disorders	-	-	-
Renal	-	-	-
Cardiac disorders	-	-	-
Acute kidney injury, creatinine increased	1	2	-
Allergic reaction and anaphylaxis	-	-	-

further studies. Recently, Di Tano and colleagues showed that non-toxic fasting-mimicking diets improve IVC effectiveness.<sup>34</sup> All these data support that if we add integrative cancer therapies to molecular-based personalized treatments, we can achieve much better results.

Our 8-patient clinical data, given the previous single agent PARPi experience, suggested that better results can be achieved with combination of ascorbate plus PARPi. Therewithal, our observation showed that IVC plus PARPi was well-tolerated, particularly in elderly patients with normal cardiac and renal function. The case series results suggest that high-dose Vit C may improve the effectiveness of PARPi and reduce its side effects, as well as prevent PARPi resistance.

## Conclusion

The combinatorial therapy involving IVC and PARPi displayed appreciable clinical outputs in the presented 8-patient

observational study. It was anticipated from the present study that chemorefractory, heavily pre-treated, or elderly patients may be suitable candidates for the combination therapy of PARPi plus IVC with HRR deficiency. On the other hand, the addition of IVC to the combination of chemotherapy plus PARPi can expand the combinations therapeutic window. Proper dosages and persistent use of PARPi are crucial for the efficacy of PARPi. However, the associated selective cytotoxicity holds primal concern. Therefore, the administration of IVC has direct cytotoxic effects that can add therapeutic value to PARPi. This therapy may mitigate side effects associated with the cancer treatment. To fully endorse our results, broader cohorts of patients should be reviewed to support our preclinical data and mechanistic hypothesis. Following, clinical studies involving a large group of a patient population utilizing the above stated combinatorial therapy regimen, we would have a clearer view to whether this combinatorial therapy could add value to the pre-existing treatment model and improve survival rate with reduced adverse effects in patients.

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## Declaration of Conflicting Interests

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