Impact of COVID-19 on medical treatment patterns in gynecologic oncology: a MITO group survey

Raffaella Cioffi,1 Giulia Sabetta,1 Emanuela Rabaiotti,1 Alice Bergamini,2 Luca Bocciolone,1 Giorgio Candotti,1 Massimo Candiani,1 Giorgia Valabrega,2 Giorgia Mangili,1 Sandro Pignata,3 on behalf of MITO group

HIGHLIGHTS
• The COVID-19 pandemic presented challenges for the clinical care of patients with gynecological cancer.
• Eighty-three percent of respondents perform COVID-19 swabs once a month in cancer patients.
• Seventy-three percent of respondents suspended oncological treatment in patients testing positive for COVID-19.

ABSTRACT
Objective COVID-19 is a global public health emergency. The increasing spread of COVID-19 presents challenges for the clinical care of patients with gynecological tumors. The Multicenter Italian Trials in Ovarian cancer and gynecologic malignancies (MITO) performed a survey to evaluate the impact of the COVID-19 pandemic on medical treatment of gynecological cancer, with a focus on chemotherapy and oral treatment with poly(ADP-ribose) polymerase inhibitors (PARP-i).

Methods The survey consisted of a self-administered online questionnaire, sent via email between November 2020 and January 2021 to all members of MITO group.

Results Forty-nine centers completed the questionnaire. The majority of respondents (83%) use screening tests to determine COVID-19 status in patients who were to undergo chemotherapy or oral medications. All respondents to our survey continued cancer therapy in patients who tested negative for COVID-19 during the pandemic. Seventy-three percent of respondents declared they stopped treatment with chemotherapy or PARP-i only after a positive swab and resumed therapy when negative tests were confirmed.

Conclusions COVID-19 positivity impacted patterns of treatment in patients diagnosed with ovarian cancer within the MITO group. Further investigations are needed to evaluate whether these modifications influence oncological clinical outcomes.

INTRODUCTION
On March 11, 2020 the World Health Organization (WHO) announced that the outbreak of the “COrona-Virus Disease 2019” (COVID-19), that initially started in Asia, had become a pandemic.1 Severe Acute Respiratory Syndrome-Coronavirus 2 (SARS-CoV-2) infection manifests itself across a wide clinical spectrum, encompassing absence of symptoms, mild upper respiratory tract disease, and severe pneumonia.2 3 Prognosis depends on several clinical factors, the most of which include older age, co-morbidities, and angiotensin-converting enzyme (ACE2) expression.4 Due to higher ACE2 expression and generally poorer health status, cancer patients are more vulnerable to the infection5 and are potentially subject to an increased risk of death.6–8 A number of case series from China reported that patients undergoing chemotherapy or surgery in the month prior to the diagnosis of COVID-19 had a higher risk of serious clinical events.7 This raised concerns among the medical community and led to a debate regarding the need to modify the management of cancer patients during the pandemic.7

Current knowledge on the impact of SARS-CoV-2 infection in patients with gynecological cancers is still scarce. Although several studies address the implications of COVID-19 on surgery, few data are available on the impact of COVID-19 on medical cancer therapy, including chemotherapy and molecular target therapies.1 10 Recently, the landscape of ovarian cancer treatment has changed due to the introduction of poly(ADP-ribose) polymerase inhibitors (PARP-i).11 Improvement of progression-free survival in randomized phase III trials led to the approval of olaparib, niraparib, andrucaparib in the setting of maintenance of newly diagnosed or relapsed platinum-sensitive ovarian cancer and as monotherapy of recurrent disease.12–14

Currently, little is known about the interaction of COVID-19 with PARP-i treatment and there are no clinical guidelines in case of incidental infection. In Italy, despite the implementation of drastic national containment, the number of COVID-19 cases remains high. In this scenario, in 2020 Italian gynecological oncologists were invited to participate in a survey organized by the Italian Society of Gynecology and Obstetrics (SIGO) and Multicenter Italian Trials in Ovarian cancer and gynecologic malignancies (MITO) to assess the impact of COVID-19 on surgical
treatment of gynecological malignancies and measures undertaken to reduce the risks of COVID-19 infection. The goal of our survey, conversely, was to evaluate the impact of COVID-19 on medical treatment of gynecological cancer, with a focus on chemotherapy and oral treatment with PARP inhibitors.

METHODS

MITO internal review board approved this study. In order to collect data about medical practice in the context of the COVID-19 pandemic in Italy, a specific survey was developed by our research center. The survey consisted of a self-administered online questionnaire, sent to physicians via email between November 2020 and January 2021. The intended population included physicians working in the field of gynecological oncology affiliated with the MITO group at the time of the survey. The main objective of the investigation was to evaluate the impact of COVID-19 on chemotherapeutic treatment and oral treatment with PARP inhibitors in ovarian cancer. Specifically, the survey included two sections: the first section assessed the personal characteristics of the respondents. The second section included questions related to the impact of COVID-19 on the practice of chemotherapy administration and treatment with PARP inhibitors for the management of ovarian cancer (Box 1). Descriptive statistics were used to analyze the data. Results are expressed as frequency, percentages, or mean±SD, as appropriate. Statistical analysis was performed with SPSS version 26 for Mac.

RESULTS

Overall, 49 centers completed the questionnaire covering the impact of COVID-19 on chemotherapy and 37 centers completed the PARP-i and COVID-19 questionnaire. Respondents to the chemotherapy and COVID-19 questions classified as medical oncologists and gynecological oncologists in 71.4% and 28.6% of cases, respectively, while respondents to the PARP-i and COVID-19 questions classified as medical oncologists and gynecological oncologists in 73% and 27% of cases; respectively. On average, the age of doctors interviewed for the chemotherapy section was 48.9 (range 31–66) years, while for the PARP-i section this was 50.1 (range 29–64) years.

Chemotherapy and COVID-19

In case of asymptomatic SARS-CoV2 infection in patients undergoing chemotherapy, 83.7% of respondents would suspend the treatment, 10.2% would continue chemotherapy, and the remaining 6.1% would modify their behavior depending on the type of treatment (Figure 1). In case of ongoing chemotherapy in asymptomatic patients who tested positive for SARS-CoV2 infection, 60% of respondents would not change their usual clinical management, while 40% would intensify clinical monitoring (Figure 2). If the patient were to be mildly symptomatic for SARS-CoV2 infection, 83.7% of respondents would interrupt chemotherapy until testing was negative, 4% would stop until symptoms disappear, 2% would modify their behavior, while 10.3% would continue chemotherapy (Figure 3). If the patient were to be moderately symptomatic for SARS-CoV2 infection, 92% of respondents would stop chemotherapy until the swab is negative, 6% would stop until symptoms disappear, and 2% would modify their behavior (Figure 3). In case of continuation of chemotherapy in mildly/moderately symptomatic

Box 1

<table>
<thead>
<tr>
<th>Chemotherapy and COVID-19</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. What would you do in case of SARS-CoV2 infection in asymptomatic patients undergoing chemotherapy?</td>
</tr>
<tr>
<td>2. If you decide to continue chemotherapy in the asymptomatic SARS-CoV2 patient, how would you act?</td>
</tr>
<tr>
<td>3. What would you do in case of SARS-CoV2 infection if the patient was slightly symptomatic?</td>
</tr>
<tr>
<td>4. What would you do in case of SARS-CoV2 infection if the patient was moderately symptomatic?</td>
</tr>
<tr>
<td>5. If you decide to continue chemotherapy in the symptomatic patient, how would you act?</td>
</tr>
<tr>
<td>6. Do you think screening for SARS-CoV2 infection is useful during chemotherapeutic treatment?</td>
</tr>
<tr>
<td>7. If yes, how often?</td>
</tr>
<tr>
<td>8. During this period have you modified blood tests and/or clinical evaluations in patients undergoing chemotherapy?</td>
</tr>
<tr>
<td>9. If yes, for which set of patients were blood tests intensified?</td>
</tr>
<tr>
<td>10. Have you had patients with a positive swab for SARS-CoV2 during chemotherapy?</td>
</tr>
<tr>
<td>11. Have you requested hospitalization?</td>
</tr>
<tr>
<td>12. Have you suspended treatment as a result of the positive results?</td>
</tr>
<tr>
<td>13. If not, have you changed the schedule of the exams during therapy?</td>
</tr>
<tr>
<td>14. If yes, how did you change the exam schedule?</td>
</tr>
<tr>
<td>15. When did you resume chemotherapeutic treatment?</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PARP-i and COVID-19</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. What would you do in case of SARS-CoV2 infection if the patient in PARP-i therapy was asymptomatic?</td>
</tr>
<tr>
<td>2. If you decide to continue PARP-i therapy in the asymptomatic SARS-CoV2 patient, how would you act?</td>
</tr>
<tr>
<td>3. What would you do in case of SARS-CoV2 infection if the patient was paucisymptomatic?</td>
</tr>
<tr>
<td>4. What would you do in case of SARS-CoV2 infection if the patient was moderately symptomatic?</td>
</tr>
<tr>
<td>5. If you decide to continue PARP-i therapy in the symptomatic patient, how would you act?</td>
</tr>
<tr>
<td>6. Do you think that screening for SARS-CoV2 infection is useful during treatment with PARP-i?</td>
</tr>
<tr>
<td>7. If yes, how often?</td>
</tr>
<tr>
<td>8. During this period have you changed blood tests and/or clinical evaluations in patients on PARP-i who are not suffering from SARS-CoV2?</td>
</tr>
<tr>
<td>9. If yes, for which set of patients were blood tests and/or clinical evaluations intensified?</td>
</tr>
<tr>
<td>10. Have you had patients with a positive swab for SARS-CoV2 during PARP-i therapy?</td>
</tr>
<tr>
<td>11. Have you requested hospitalization?</td>
</tr>
<tr>
<td>12. Have you suspended treatment as a result of the positive results?</td>
</tr>
<tr>
<td>13. If not, have you changed the schedule of the exams during therapy?</td>
</tr>
<tr>
<td>14. If yes, how did you change the exam schedule?</td>
</tr>
<tr>
<td>15. When did you resume PARP-i therapy?</td>
</tr>
</tbody>
</table>

COVID-19, COronaVIrus Disease 2019; PARP-i, poly(ADP-ribose) polymerase inhibitors; SARS-CoV2, Severe Acute Respiratory Syndrome Coronavirus 2.
patients, 92% of respondents would intensify clinical monitoring and 8% would not change the usual clinical management.

With respect to COVID-19 testing, together with accurate collection of medical history and physical examination, 61% of respondents believed that screening for SARS-CoV2 infection during chemotherapy is useful (Figure 4). Specifically, 83% of respondents perform the screening test at least once a month. During COVID-19 pandemic, only 18.4% of physicians modified blood tests and/or clinical assessments in patients receiving chemotherapy. In particular, 56% intensified assessments in patients with co-morbidities and/or advanced cancer while 44% intensified clinical evaluations for all patients.

The following data refer to the clinical experience of Italian oncologists in 2020. Since the beginning of the pandemic, 65% of respondents had asymptomatic SARS-CoV2 patients undergoing chemotherapy, 16% had moderately symptomatic SARS-CoV2 patients, while the remaining 19% had no cases of cancer patients affected by COVID-19. Only for 17.5% of the respondents with SARS-CoV2 positive patients did the infection required hospitalization. Following the finding of positivity to SARS-CoV2, 73.5% of respondents suspended chemotherapy. Among those who have not stopped treatment, only 6% changed their blood tests schedule, either by increasing frequency (33%) or by increasing the number of blood tests and frequency (67%). Ninety-one percent of physicians with COVID-19-positive patients resumed cancer treatment when testing was negative, while the remaining 9% resumed chemotherapy only after symptom resolution.

**PARP Inhibitors and COVID-19**

As for PARP-i therapy, 59.5% of respondents would stop therapy until testing was negative in asymptomatic patients and 40.5% would continue treatment (Figure 1). Of the latter, 46.7% would not change clinical management, 33.3% would intensify the schedule of blood tests, while the remaining 20% would proceed differently (Figure 2). In case of slightly or moderately symptomatic SARS-CoV2 infection, only 13.5% and 8%, respectively, would continue therapy. Instead, 70.3% of respondents would stop treatment until testing was negative (Figure 3). All those deciding to continue therapy in symptomatic SARS-CoV2 patients would intensify the schedule of blood tests. Approximately half of the respondents (51.4%) considered screening for SARS-CoV2 infection to be useful during PARP-i therapy.

---

**Figure 1** Q1: What would you do in case of SARS-CoV2 infection in asymptomatic patients undergoing chemotherapy/PARP-i? PARP-i, poly(ADP-ribose) polymerase inhibitors; SARS-CoV2, Severe Acute Respiratory Syndrome-Coronavirus 2.

**Figure 2** Q2: If you decide to continue chemotherapy/PARP-i in the asymptomatic SARS-CoV2 patient, how would you act? PARP-i, poly(ADP-ribose) polymerase inhibitors; SARS-CoV2, Severe Acute Respiratory Syndrome-Coronavirus 2.

**Figure 3** Q3: What would you do in case of SARS-CoV2 infection if the patient was paucisymptomatic? Q4: What would you do in case of SARS-CoV2 infection if the patient was moderately symptomatic? PARP-i, poly(ADP-ribose) polymerase inhibitors; SARS-CoV2, Severe Acute Respiratory Syndrome-Coronavirus 2.

**Figure 4** Q6: Do you think that screening for SARS-CoV2 infection is useful during treatment with chemotherapy/PARP-i? PARP-i, poly(ADP-ribose) polymerase inhibitors; SARS-CoV2, Severe Acute Respiratory Syndrome-Coronavirus 2.
treatment (Figure 4). Specifically, 89.5% who would perform it on a monthly basis.

Regarding the management of patients treated with PARP-i who were not affected by COVID-19, 94.9% of respondents would not change blood work and/or clinical assessments. Half of the physicians choosing to intensify clinical/blood monitoring would only do it for patients with co-morbidities. Overall, 29.7% of respondents had patients testing positive for SARS-CoV2 during treatment with PARP inhibitors, but none required hospitalization. However, 72.2% suspended the treatment following positive testing and only resumed treatment after a negative test result. Among physicians deciding not to stop treatment, 87.5% changed the anamnestic questionnaire before treatment administration, while the remaining 12.5% modified the form by adding further exams.

DISCUSSION
Summary of Main Results
This survey shows how COVID-19 positivity impacted patterns of treatment in patients diagnosed with ovarian cancer within the MITO group. In particular, 83% of physicians decided to perform COVID-19 swabs once a month and 73% suspended oncological treatments in patients testing positive for COVID-19.

Results in the Context of Published Literature
As COVID-19 is continuing to spread globally despite strict security measures implemented by many countries, growing concerns arise on the impact of SARS-CoV2 on cancer care. To date, few studies on cancer patients affected by COVID-19 are available.16 Oncological patients seem to be a highly vulnerable subgroup in this pandemic. The COVID-19 death rate is twice as high in cancer patients compared with the general population (5.6% vs 2.3%).5 Although reported mortality rates are very variable depending on co-morbidities, performance status, and type of cancer.17 Meng et al reported that hospitalized SARS-CoV2 patients with cancer have a higher death rate than SARS-CoV2 patients with no history of cancer (29.4% vs 10.2%).18 This higher risk could depend on post-surgery outcomes, immunological deficiency due to antitumor therapy, or inflammation in the tumor microenvironment.18

Patients undergoing surgery and general anesthesia have a greater risk of contracting SARS-CoV2 infection, while data on the risks associated with chemotherapy and oral maintenance therapies in cancer patients are currently scarce and conflicting.19 The detrimental effects of anticancer drugs on humoral immunity and neutrophil count and function are well known. However, immunosuppression by itself is not enough to justify the increased risk of critical lung disease observed in oncological patients.19 Some conditions of cancer patients, such as as anemia and hypoproteinemia, can also affect the immune system and increase the susceptibility to infectious respiratory pathogens.9

Conversely, the reduced activity of cytokines and the typical immunosuppressive state in cancer patients could paradoxically be beneficial in the context of a COVID-19 infection. In some patients, a cytokine storm is elicited by high viral titers. Cytokines, such as interleukin (IL)-6, IL-8, and IL-1β, are responsible for immunopathogenic damage to the lungs and multorgan failure.20–22 Two Chinese studies showed that recent cytotoxic chemotherapy was associated with increased mortality.23 24 Conversely, a French study reported that the administration of chemotherapy in the 3 months prior to the diagnosis of COVID-19 was not associated with increased disease severity.17 Another cohort study including 281 cancer patients who underwent chemotherapy 1 month before COVID-19 infection reports a death rate of 27% versus 29% in patients not undergoing chemotherapy.25 Therefore, it could be inferred that cytotoxic chemotherapy is not a relevant risk factor for mortality in COVID-19 infection. Likewise, patients who received different anticancer treatments (such as immunotherapy, hormonal therapy, radiotherapy, and targeted therapies) did not show an increased mortality for COVID-19 infection.25

The use of some antiblastic drugs such as topoisomerase II inhibitors and alkylating agents seems to be protective against SARS-CoV2 infection.26 Some reports suggested continuing targeted therapies, such as ALK/ROS1 tyrosine kinase inhibitors in patients with lung cancer and COVID-19 infection, as a high risk of cancer exacerbation after treatment discontinuation, with rapidly progressive course, has been observed.27 In line with this, all respondents to our survey continued cancer therapy in patients who tested negative for SARS-CoV2 during the pandemic. More than 70% of respondents declared that they stopped treatment with chemotherapy or PARP inhibitors only after a positive test and resumed therapy once testing was negative. In the French cohort, COVID-19 was responsible for a temporary or definitive discontinuation of cytotoxic chemotherapy in 39% of patients and a change of chemotherapy regimen in 5% of cases.17

Some studies warn about the risk that, as a consequence of treatment-related immune suppression, cancer patients might not develop COVID-19 symptoms.28 In addition, use of corticosteroids in these patients could also cover the first signs of a SARS-CoV2 infection. Therefore, a careful approach including patient testing with swabs or antigen tests on a regular basis is recommended.29 In our study, the majority of respondents (83%), in addition to carrying out an accurate patient interview, use screening tests such as nasopharyngeal swab to search for SARS-CoV2 infection in patients who need to undergo chemotherapy or oral medications. In most Italian MITO centers, COVID-19 testing is scheduled on a monthly basis. For the same reason, in case of ongoing therapy with chemotherapeutics or PARP-i in asymptomatic patients with a positive test, clinical monitoring was intensified in 40% and 33.3% of cases, respectively.

It has been shown that PARP-i can have beneficial effects on SARS-CoV2 infection, by preventing both macrophage hyperactivation and subsequent cytokine storm.30 PARP-i may also enhance the efficacy of therapy with tocilizumab, anakinra, sarilumab, adalimumab, canakinumab, or siltuximab, which are used in the treatment of symptomatic SARS-CoV2 infection.30 The majority of respondents to our survey (73%) suspended treatment with a positive testing. However, none of the patients treated with PARP-i developed severe disease requiring hospitalization. Ninety-five percent of respondents did not increase the amount of clinical and laboratory assessments in patients treated with PARP-i, probably to minimize their exposure to the hospital environment which has always been considered a high risk of contagion.

Strengths and Weaknesses
This survey fills a knowledge gap by illustrating the medical management of gynecological cancers in Italy in 2020, particularly
focusing on chemotherapy and oral maintenance treatment. However, it has several limitations. First, most of the questions in our survey are closed-ended, so they do not capture the full range of practical behaviors of respondents. However, this method was chosen to avoid the heterogeneity of answers to open-text questions which can complicate analysis and interpretation of results. Second, our results may be affected by omitted answers. Last, but not least, the COVID-19 outbreak is a rapidly evolving situation; therefore, behaviors in clinical practice are constantly changing.

Implications for Practice and Future Research

According to our survey, 17% of patients with gynecological malignances affected by COVID-19 required hospitalization. Cancer patients diagnosed with COVID-19 should be closely monitored, regardless of the severity of their symptoms, and preventive measures to minimize the risk of patient exposure to SARS-CoV-2 should be taken. However, it is also crucial to avoid under-treatment and treatment delays as much as possible. Several case series reported how this could be a factor increasing cancer morbidity and mortality, perhaps much more than COVID-19 itself. In this context, it is our aim to correlate clinical outcomes of patients affected by gynecological malignancies according to pattern of treatment within MITO group.

CONCLUSIONS

The results of this survey show that gynecological oncology departments have promptly set up an active approach in managing COVID-19 and its repercussions on clinical practice. However, they also show that there is still a great deal of discrepancy in the therapeutic management of oncological patients affected by COVID-19 in Italy, especially if they are asymptomatic. Univocal national guidelines are urgently needed for the management of cancer patients undergoing chemotherapy or oral maintenance in case of positive COVID-19.

Acknowledgements

The authors thank all the members of MITO group for participating in the survey.

Collaborators


Contributors

RC: writing – original draft, review and editing. GS: formal analysis; writing – original draft. ER, AB, LB, GC: conceptualization; data curation. MC: supervision. GV, GM, SP: conceptualization; methodology; supervision.

Funding

The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests

None declared.

Patient consent for publication

Not required.

Ethics approval

MITO internal review board approved this study.

Provenance and peer review

Commissioned; externally peer reviewed.

Data availability statement

Data are available upon reasonable request. Deidentified participant data are stored in San Raffaele Hospital archives and can be provided upon reasonable request by contacting the corresponding author (mangili.giorgia@hsr.it).

This article is made freely available for use in accordance with BMJ’s website terms and conditions for the duration of the covid-19 pandemic or until otherwise determined by BMJ. You may use, download and print the article for any lawful, non-commercial purpose (including text and data mining) provided that all copyright notices and trade marks are retained.

ORCID iD

Alice Bergamini http://orcid.org/0000-0002-1915-8313

REFERENCES

Original research


