Systematic Review

Pressurized intraperitoneal aerosol chemotherapy (PIPAC) in treatment of advanced ovarian cancer. A review of the literature

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Abstract

Objective: The majority of advanced ovarian cancer (OC) patients do not fully respond to systemic chemotherapy, thus complete cytoreduction cannot be achieved in such cases. Pressurized intraperitoneal aerosol chemotherapy (PIPAC) has been suggested as an alternative approach for these women. Our study aimed to review the literature regarding the application of pressurized intraperitoneal aerosol chemotherapy (PIPAC) in OC patients with peritoneal carcinomatosis (PC). Data source: Articles in the English language were searched in PubMed. Search terms included “PIPAC” and “ovarian cancer”. Methods of study selection: The authors evaluated all studies presenting an application of pressurised intraperitoneal aerosol chemotherapy (PIPAC) on ovarian cancer patients. The published guidelines for Systematic Reviews and Meta-analyses (PRISMA) were followed in the present systematic review which was performed based on the authors’ predetermined inclusion criteria. Tabulation: Table 1 presents the main characteristics and outcomes of the OC patients undergoing PIPAC. Integration: Study selection and data extraction were independently undertaken by two reviewers. Results: 235 patients from 15 studies retrieved from PubMed were included. Conclusions: Our results indicate that PIPAC is efficient and safe in selected OC patients with PC not responding to systemic chemotherapy. The toxicity is manageable and the quality of life sustained. Further, randomised controlled trials are warranted to confirm our findings.

Keywords: Pressurized intraperitoneal aerosol chemotherapy; PIPAC; Ovarian cancer; Peritoneal metastasis

1. Introduction

Management of peritoneal carcinomatosis of gynecological origin is challenging, despite the great progress in the fields of surgery, chemotherapy and immunotherapy, resulting in poor prognosis and low survival rates, in comparison with patients with parenchymatous metastases. The standard of care for advanced ovarian cancer patients with peritoneal metastasis (PM) is based on complete cytoreduction surgery (CRS) combined with systemic therapy. Hence, the response to systemic intravenous chemotherapy is poor, not only because of molecular mechanisms, but mainly because the drug penetration of systemic chemotherapy into the peritoneal metastases is low. Intraperitoneal chemotherapy has been proved to be an alternative approach for such cases [1].

Interestingly, systemic chemotherapy, often followed by maintenance therapy, is also the suggested treatment for ovarian cancer recurrences, although some selected patients seem to also benefit from a preceding secondary debulking. However, multiple lines of palliative systemic chemotherapy are usually the final management for patients with relapses, related unfortunately to significant toxicity depressing their quality of life while on the other hand no clear benefit has been demonstrated when they are applied beyond the third line [2]. It is therefore clear that alternative treatment options are needed for ovarian cancer patients with peritoneal metastases, recurrent disease or both, especially for women unwilling or unable to receive palliative chemotherapy. Intraperitoneal chemotherapy (IPC) has been demonstrated to be effective against peritoneal dissemination, although its indications are not yet fully clarified and its toxicity is also significant. More specifically, regarding ovarian cancer, the role of combined CRS with hyperthermic intraperitoneal chemotherapy (HIPEC) has been very controversial, despite growing evidence about its efficacy, mainly because of the high morbidity and mortality rates following these procedures [3]. In that setting, pressurized intraperitoneal aerosol chemotherapy (PIPAC), a new type of pressurized IPC, is a promising variant, aiming to achieve deeper perforation of the chemotherapy regimens applied in the form of aerosol into the peritoneum, being better tolerated and less invasive. The aim of our study is to review the data regarding the application of PIPAC on patients with ovarian cancer and peritoneal metastases, and evaluate the feasibility, safety and efficacy of the method.

2. Materials and methods

2.1 Data sources

Two independent authors (VP, AF) searched the literature up to July 2021 using the key words: (PIPAC) and (ovarian cancer) as search terms. The inclusion criteria were clearly specified and no discrepancies in the results were reported.
2.2 Study selection criteria
Our review included all studies presenting an application of pressurized intraperitoneal aerosol chemotherapy (PIPAC) on ovarian cancer patients. Animal studies, manuscripts presented in scientific conferences or studies written in languages other than English, German and Greek were excluded.

2.3 Selected studies
A total of 48 studies were retrieved, 12 of which were considered to be eligible for inclusion in our review. 28 studies were excluded according to specific criteria (reviews, letters, editorials, conference papers) and 4 studies in languages other than English were excluded. Additionally, another 3 studies were excluded from our review, since they were performed on animals. Finally, studies describing a combination of PIPAC with other methods or heated intraperitoneal chemotherapy (HIPEC) were excluded from our study too. The PRISMA flow diagram schematically presents the stages of article selection (Fig. 1).

3. Results
Table 1 summarizes the data collected from studies [2–15] referring to the application of PIPAC on ovarian cancer patients.

We evaluated a total of 235 patients, with a median age of 73.5 years old (60–84). 78 (33.1%) of the patients were treated because of recurrent disease. The median Peritoneal Cancer Index (PCI) was 17 (14–20) and the histological type of the malignancy was serous in 63 patients (26.8%), mucinous in 2 (0.8%) of the patients, 4 patients (1.7%) had other histological types, while 163 (69.4%) patients had recurrent disease and on the histology is not defined in the rest 3 women. Regarding the PIPAC application, the mean number of courses needed was 9 (6–13) and the mean hospital stay was 3 days. In the majority of the cases, a combination with cisplatin and doxorubicin was used, since it is referred to be applied on 117 (49.8%) of the patients, while the rest of the studies do not clarify the regiment used on the rest 118 patients.

Improvement was observed in the majority of the patients, since in 73 (31.1%) of the patients histological response was demonstrated, while in another 76 (32.3%) a
are disappointing, mainly because of ineffective intraperi-
toinal distribution of the regiments and poor pharmacoki-
netics. Additionally, systemic chemotherapy is accompa-
nied by high toxicity, tremendously reducing the quality of
life of the patients [16].

PIPAC is a new approach of intraperitoneal chemotherapy offering augmented coverage of the peritoneal surface and deeper drug delivery into intraperi-
toanal tumor nodules, without the toxicity of systematic chemotherapy, since it requires almost the 1/10 of the
drug dose. Among other advantages of the method, the fast learning curve and the possibility of co-administration
with systematic therapy or as a monotherapy in multiple applications every 6–8 weeks. The application of PIPAC is a
minimally invasive technique utilizing aerosol, instead of
the classic liquid chemotherapy regimens, under increased
hydrostatic pressure and was first introduced by Prof. Marc
Reymond in Germany [17].

Currently, PIPAC is still being under evaluation as an
experimental therapy either for patients with peritoneal car-
cinomatosis that are not eligible for systematic chemother-
apy or for those who have already undergone multiple lines
of chemotherapy and have been burdened with significant
toxicity. Moreover, Tempfer et al. [5] have highlighted
particularly promising results in cases of platinum-resistant
ovarian cancer. In our findings, the median age is relatively
high at 73 years, compared to other EOC studies, and it is
more reflective of a geriatric age, indicating that PIPAC can
also be offered as an alternative of a palliative therapy.

We reviewed the literature up to July 2021 in order to
clarify the efficacy and safety of the method, with regards
to its application in ovarian cancer patients with peritoneal
metastases.

Based on our results from the analysis of 12 studies
presenting cases of PIPAC application in women with ovar-
ian cancer and peritoneal metastasis, PIPAC could be con-
sidered an effective alternative treatment for such cases,
achieving a histological response of 31% and a PCI im-
provement in 32.3% of the cases, with a complication rate
CTCAE ≥2 of 26.3%, which despite not being low, is how-
ever accompanied with no toxicity in the majority of the
studies and excellent quality of life.

Tempfer et al. [13–16], meticulously studied the ap-
plication of PIPAC in several women with ovarian cancer
and peritoneal carcinomatosis. First, in 2015, they con-
ducted a cohort study including 53 women receiving PIPAC
with 33 of them achieving a histological response and 26 a
PCI improvement, while OS and PFS reached up to 331 and
144 days respectively [14]. In 2018 [11], the same team
presented a study where 85 women with peritoneal carci-
nomatosis were treated with PIPAC. 38 of them had hist-
ological response and 32 improved PCI, while in the pre-
vvious year a 75 years old patient successfully received 13
courses of PIPAC against a recurrent serous ovarian cancer
with notable tumor response [13]. In their latest study in
2018, 25 of the 27 women included, suffered also from re-

<table>
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<th>Table 1. Main characteristics and outcomes of the ovarian cancer patients undergoing PIPAC.</th>
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<tbody>
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<td>Demographics</td>
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<td>Age (median, range)</td>
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<td>Peritoneal Cancer Index (median, range)</td>
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<td><strong>Histology</strong></td>
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<td>Mucinous</td>
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<td>Recurrent disease</td>
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<td>Number of PIPAC courses</td>
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<td>Mean hospital stay</td>
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<td><strong>Regimens</strong></td>
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<td>Cisplatin and doxorubicin</td>
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<tr>
<td>Cisplatin</td>
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<tr>
<td>Not specified</td>
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<tr>
<td>Histological response</td>
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<td>PCI improvement</td>
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<td>Stable disease</td>
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<td>Disease progression</td>
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PCI improvement was noticed. Only in 29 women (12.3%)
the disease remained stable when 41 (17.4%) had a disease
progression. Median overall (OS) and progression free sur-
vival (PFS) was 212.3 (102–331) and 144 (14–144) days
respectively with a median follow-up period of 8.8 months
(3–22). Quality of life was declared as satisfying by most
women in terms of low toxicity and high rates of Quality-
of-life-scores, which were described narratively in the ma-
ajority of the studies.

Concerning the complications of the method, using
the score of the Common Terminology Criteria for Adverse
Events (CTCAE), major complications (CTCAE ≥2) were
observed in 62 (26.3%) women.

4. Discussion

It is without doubt, that the standard treatment for in-
operable ovarian cancer patients with peritoneal carcino-
matisis is based on systemic chemotherapy. However, the
response rates after three lines of chemotherapy or even
two lines when it comes to platinum-resistant recurrences
are disappointing, mainly because of ineffective intraperi-
current ovarian cancer and a mean PCI of 20.4, however the application of PIPAC resulted in a PCI improvement in 15 of them [14].

Apart from the case report presented from Tempfer et al. [13], Solass et al. [15] presents a case of an elderly woman with PCI of 14 receiving 6 courses of PIPAC with cisplatin/doxorubicin and presenting histological response and PCI improvement with an excellent quality of life. Giger-Pabst also presents an 84-years old receiving 8 courses of PIPAC with the same regimens and histological response without any toxicity [4], while Alyami et al. [7] present 4 similar cases.

Cisplatin and doxorubicin combination is the most commonly used pharmacological regimen, applied to 117 (49.8%) of the patients. Interestingly, Sgarbura et al. [8] present the application of oxaliplatin in 5 patients with a mean PCI of 18, reaching an OS of 122 days. Lately, Siebert et al. [9] published a single center comparative study, where PIPAC was combined with systemic chemotherapy and bevacizumab in 21 women, impressively reaching a mean OS of 204 days.

Regarding the survival, it is unfortunately impossible to draw conclusions about PFS and OS in such a heterogeneous population. In our study we attempted to separate the survival times by primary vs recurrent EOC patients. Our findings suggest that the median OS of patients receiving PIPAC as a primary management reach 6.8 months, while when PIPAC is applied in OC patients with recurrent disease, the OS reaches 11 months with a PFS of 5 months.

To our knowledge, our study is the first so far, presenting the outcomes of the application of PIPAC on ovarian cancer patients. Our results indicate that PIPAC is a feasible and safe treatment option for well selected patients. Hence, before reaching safe conclusions, several limitations need to be considered. Firstly, the number of the included studies is small, resulting in a small total number of enrolled women. Secondly, the evaluated parameters are various and thus the heterogeneity of the included studies is wide. Additionally, the lack of specific data regarding the histological type of the ovarian cancer patients that are included in many of the studies is making conclusions difficult to draw. The majority of these studies reporting on survival did not stratify their results for patients receiving PIPAC as primary versus recurrence treatment, and some studies reporting tumor response did not provide definitions of response and progression.

Last but not least, all the included studies are retrospective or cases reports, since to this point no randomized controlled trials are running. Moreover, the efficacy of the method is not described by RECIST criteria, which were not reported in the retrospective data.

5. Conclusions

In conclusion, PIPAC presents the effort to provide advanced ovarian cancer patients suffering from peritoneal metastases or relapses and unable or unwilling to undergo systemic chemotherapy or beyond the third line of it, an alternative management that is effective, safe and associated with lower toxicity and higher quality of life. Large clinical trials are warranted to establish the indications, the eligible regimens and the optimal dose as well as the number of courses needed.

Author contributions

VP—Data collection, data management and analysis, consultation to the manuscript. AF—Data collection and management, manuscript writing. AP—Data collection and management, manuscript writing. CI—Protocol/project development, data management, consultation to the manuscript.

Ethics approval and consent to participate

Not applicable.

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Conflict of interest

The authors declare no conflict of interest. Christos Iavazzo is serving as one of the Editorial Board members of this journal. We declare that Christos Iavazzo had no involvement in the peer review of this article and has no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to Enrique Hernandez.

References

Pressurized intraperitoneal aerosol chemotherapy (PIPAC) is a novel treatment approach for patients with peritoneal carcinomatosis. This technique involves the administration of chemotherapeutic agents in a pressurized aerosol form directly into the peritoneal cavity, allowing for high drug concentrations in the peritoneal cavity with minimal systemic exposure. This approach aims to improve the efficacy of chemotherapy by maximizing drug exposure to peritoneal tumors while minimizing systemic toxicity.

Several studies have explored the use of PIPAC with different chemotherapy regimens. For example, Tempfer et al. (2015) conducted a phase 2 study examining pressurized intraperitoneal aerosol chemotherapy (PIPAC) in women with recurrent ovarian cancer. They found that PIPAC was safe and well-tolerated, with promising responses in patients who had not previously received chemotherapy.

Alyami et al. (2021) treated unresectable peritoneal metastasis by combining PIPAC with cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. This approach resulted in successful cytoreduction and long-term survival in a higher proportion of patients compared to conventional chemotherapy alone.

Sgarbura et al. (2019) investigated the use of oxaliplatin in PIPAC and found it to be safe and effective in patients with peritoneal carcinomatosis.

Other studies have explored the use of PIPAC in combination with systemic chemotherapy and bevacizumab, with promising results in terms of safety and feasibility (Siebert et al., 2021).

Kurtz et al. (2018) reported on the feasibility, safety, and efficacy of PIPAC for peritoneal metastasis in a registry study. Their findings supported the use of PIPAC as a viable treatment option for patients with peritoneal carcinomatosis.

De Simone et al. (2020) conducted a phase II clinical trial of PIPAC with oxaliplatin, cisplatin, and doxorubicin in patients with peritoneal carcinomatosis, demonstrating the feasibility and safety of the approach.

In conclusion, PIPAC represents a promising treatment modality for patients with peritoneal carcinomatosis, offering the potential for improved efficacy and reduced systemic toxicity compared to traditional chemotherapy approaches. Further research is needed to fully elucidate the benefits and limitations of PIPAC and to optimize its use in clinical practice.