Hyperthermia in Epithelial Ovarian Cancer

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Advanced ovarian cancer is the leading cause of gynecological death with a high rate of reoccurrence indicating the critical need for improved therapeutics. Hyperthermic intraperitoneal chemotherapy (HIPEC) treatment for ovarian cancer has shown efficacy in extending patient overall survival.

hyperthermia ovarian cancer immunity

1. Introduction

Epithelial ovarian, fallopian tube, and primary peritoneal cancers (EOC) are a leading cause of cancer death in women, highlighting the critical clinical need for therapeutic development [1]. The majority (80%) of EOC patients present with advanced stage (III–IV) disease and have a poor prognosis (5-year cancer stage-specific survival 42% and 26%, respectively). Standard of care treatment for advanced EOC involves a combination of debulking surgery and chemotherapy. Hyperthermia has been utilized in cancer treatment for centuries and continues in modern medicine [2]. The therapeutic strategy known as hyperthermic intraperitoneal chemotherapy (HIPEC) in EOC patients at the time of interval debulking surgery (IDS) shows promise as patients experience an extension in overall survival (OS) of nearly 12 months compared to patients undergoing interval debulking surgery (IDS) alone [3]. While this represents the most significant extension of overall survival in EOC patients in over a decade [3], HIPEC mechanisms of action have yet to be understood, thereby limiting further optimization of HIPEC for patients with advanced EOC.

2. Hyperthermia in Cancer Therapy—The Clinical Picture

2.1. Ovarian Cancer

Epithelial ovarian cancer (EOC) is an aggressive disease of the female reproductive system, often arising from the fallopian tubes, involving the surface lining (epithelial tissue) of the ovaries. A total of 1 in 78 women will experience ovarian cancer in their lifetime [4]. It is expected that more than 22,000 new cases will be reported annually, of which 14,000 will succumb to the disease [5]. EOC has the highest mortality rate of any gynecological cancer with a case-to-death ratio equivalent to lung cancer [6]. Nearly 80% of patients present in late stage (III–IV) thus resulting in poor prognosis [5]. A combination of cytotoxic platinum-paclitaxel-based chemotherapy and debulking surgery remains the standard of care for advanced EOC. While standard treatments have shown initial beneficial outcomes, 70% of patients with advanced disease will experience recurrence within five years, ultimately ending in mortality [7]. The goal of surgery for these patients is to achieve complete macroscopic cytoreduction, as this

optimizes overall survival benefit for this intervention [8][9][10]. In patients for whom upfront or primary debulking surgery (PDS) is not safe or complete macroscopic resection is not feasible, neoadjuvant chemotherapy (NACT) followed by interval debulking surgery (IDS) and postoperative chemotherapy allows for initial reduction of disease burden to optimize patients for surgical resection. Randomized clinical trials report no significant difference in progression-free survival (PFS) and overall survival (OS) with this approach compared to primary debulking surgery followed by adjuvant chemotherapy [11]. Despite several new chemotherapy agents demonstrating efficacy against EOC, minimal strides have been made to improve patient OS [11]. The need for new clinical therapeutic strategies is crucial in fighting this disease.

Hyperthermic intraperitoneal chemotherapy (HIPEC) is a promising approach to treating advanced EOC, prolonging the overall survival of patients. HIPEC treatment involves abdominal perfusion of heated chemotherapy via catheter insertion at the time of cytoreductive surgery (CRS). Perfusion machines maintain a constant infusion temperature through the abdominal cavity. Van Driel and colleagues performed a phase 3 randomized controlled trial (OVHIPEC-1) to test the benefits of HIPEC on newly diagnosed EOC patients, comparing results to treatment without HIPEC [3]. Patients with extensive disease who were not ideal candidates for primary debulking surgery (PDS) or patients with residual tumor after PDS were referred for NACT with or without HIPEC as study participants. Three cycles of NACT were completed prior to entry into the trial. Cytoreductive surgery was completed with or without intraoperative administration of HIPEC using perfusion of cisplatin heated to 40 °C for 90 min via an open abdomen technique. Following surgery, patients in both groups received an additional three cycles of chemotherapy. Results revealed patients receiving HIPEC had an extended OS by nearly 12 months, with no increased rate of adverse effects [3].

To answer the question of whether HIPEC extends patient survival regardless of the timing of cytoreductive surgery, a single-blinded randomized study was performed including patients with stage III or IV ovarian cancer planned for either PDS or IDS [12]. Patients randomized to the HIPEC arm received cisplatin heated to 41.5 °C for 90 min using the closed perfusion Belmont Hyperthermia Pump System. The results reveal an extended PFS and OS in the HIPEC cohort, with an OS increase in 8.2 months in HIPEC patients. Further exploration into any differences between HIPEC at the time of PDS or IDS revealed an increase in PFS and OS in the patients receiving HIPEC after IDS, by 2 and 13 months respectively. Notably, HIPEC at the time of PDS did not extend patient OS and PFS (**Table 1**). Consistent with Van Driel, these results indicate that HIPEC at the time of IDS prolonged patient survival and improved time to recurrence, providing further evidence of the benefit of HIPEC on extending patient survival against EOC [12].

Table 1. Summary of clinical findings indicating HIPEC survival benefit.

Author	Year	Study Type	N	Study Details	OS Benefit	PFS Benefit	RFS Benefit
Lim et al. [12]	2022	Single-Blind Randomized	184	HIPEC + interval CRS after NACT in ovarian cancer	13.6 months	2 months	N/A

Author	Year	Study Type	N	Study Details	OS Benefit	PFS Benefit	RFS Benefit
Ghirardi et al. [13]	2022	Retrospective	70	HIPEC + BRCA mutational status in EOC	No difference between BRCA status	No difference between BRCA status	N/A
Costales et al. [14]	2021	Retrospective	48	PS vs. PR EOC patients given HIPEC after CRS	median 26.9 months in PR patients	N/A	11.2 months in PS patients
Van Driel et al. [3]	2018	Open-Label Randomized	245	Interval CRS ± HIPEC for EOC	11.8 months	N/A	3.5 months
Spiliotis et al. [15]	2015	Open-Label Randomized	120	CRS ± HIPEC for recurrent EOC	13.3 months	N/A	N/A
Safra et al. [16]	2014	Case-Control Study	27	CRS ± HIPEC ± BRCA mutation in EOC	Not reached at time of analysis (70% patients alive)	9 months, no difference in BRCA status	N/A

The standard of care for advanced EOC includes cytotoxic platinum- and paclitaxel-based chemotherapy. In cases of HIPEC, however, single-agent platinum-based chemotherapies, particularly cisplatin or carboplatin, can be used [17]. Several studies have outlined variations in the efficacy of treatment based on the type of chemotherapy utilized in HIPEC. A recent prospective analysis found that PFS was significantly increased with paclitaxel/cisplatin-based HIPEC compared to single-agent cisplatin-based HIPEC [17]. These preliminary findings suggest that the combination of both chemotherapies may be superior to cisplatin alone. Overall survival data is not yet mature. Along the same line, though carboplatin and cisplatin have similar mechanisms of action [17], they can result in different patient outcomes. Zivanovic et al. demonstrated that carboplatin and cisplatin had similar safety profiles in the use of HIPEC for the treatment of recurrent ovarian cancer during secondary cytoreductive surgery [18]. Nevertheless, HIPEC with carboplatin at the time of IDS was not superior to IDS alone in terms of clinical outcomes in this study. These results illustrate that platinum-based HIPEC chemotherapy regimens have varying efficacies, particularly when used alone and when used with additional chemotherapeutic agents.

While the majority of EOC patients initially respond to platinum-based therapy, they often become platinum-resistant (PR) over time, defined as experiencing a disease recurrence within six months of platinum-based therapy [19]. The determination of platinum resistance confers poor prognosis for patients as remaining therapeutic options have limited efficacy. Several studies have suggested that PR patients receiving HIPEC had no alteration in survival rate after HIPEC compared to that of platinum-sensitive (PS) patients [14][15][20]. A randomized study by Spiliotis et al. compared OS in patients undergoing CRS with or without HIPEC for recurrent EOC [15]. Patients who received HIPEC at the time of surgery for recurrence had an OS of 26.7 months compared to 13.4 months for patients who did not receive HIPEC. Furthermore, in the HIPEC group, there was no difference in OS among PS and PR patients (26.8 vs. 26.6 months), while a statistically significant difference in OS was noted between PS and PR patients in the non-HIPEC group (15.2 vs. 10.2 months). This data suggests that HIPEC may overcome the

resistance to platinum-based chemotherapy exhibited by the stem cells harbored within recurrent disease [15]. More recently, a retrospective study compared PFS and OS in platinum-sensitive and platinum-resistant EOC patients after cytoreductive surgery (CRS) and HIPEC to determine if CRS with HIPEC in PR patients can overcome PR treatment disadvantages [14]. Patients showed an improved treatment-free interval (TFI) when treated with a combination of HIPEC and secondary CRS, regardless of platinum sensitivity. PS patients had an improved survival to a higher degree than PR patients. Complete tumor resection resulted in significantly increased PFS in PS patients. (Complete cytoreduction was associated with longer survival.) Study limitations included the low number of PR patients and lack of complete resection in nearly half the PR patients. Results suggested that the combination of CRS and HIPEC in PR patients extends the TFI and thus this combination could be a treatment option for patients with PR EOC [14]. Further inquiry is needed to evaluate the role of HIPEC in improving OS for PR patients.

It has been demonstrated that homologous recombination repair (HRR) mutations extend EOC patient PFS and OS [21]. Homologous recombination (HR) is a double-stranded DNA repair mechanism in which damaged chromosomes are repaired and cells are protected from chromosomal aberrations. Disruptions in this pathway result in homologous recombination deficiency (HRD), which impairs a cell's ability to repair the DNA damaged by chemotherapy [22]. The process of HR includes several mediator genes including BRCA1 and BRCA2; however, these are also among the most mutated HR genes and commonly present in ovarian cancer [23]. Mutations in BRCA1/2 increase the lifetime risk of ovarian cancer development by 40% [24]. Studies show EOC patients with a BRCA mutation have increased chemosensitivity, specifically to platinum-based therapeutics. BRCA mutational status similarly impacts EOC patient response to HIPEC treatment, as hyperthermia impairs the BRCA protein function [13]. An exploratory analysis of the OVHIPEC-1 trial performed by Koole et al. found that patients without BRCA mutations had an increased benefit from HIPEC when compared to those with BRCA mutations [25]. The researchers evaluated tissue samples and tumor DNA from 200 patients with stage III ovarian cancer originally enrolled in the trial and categorized them by BRCA status and HRD status based on copy number variation profile. This study found no significant recurrence-free survival (RFS) benefit or OS benefit to HIPEC among patients with BRCA mutations, HR 1.25 (99%CI 0.48–3.29) and 1.94 (99%CI 0.42–9.16), respectively. Conversely, patients with HRD/BRCA wild-type tumors demonstrated an RFS benefit from HIPEC, HR 0.44 (99%CI 0.21–0.91) without OS benefit 0.55 (99%CI 0.23–1.30). HRD classification may play an increasing role in selecting optimal patients for HIPEC therapy.

The reduction of recurrence seen from HIPEC treatment is promising as the majority of patients with advanced disease experience recurrence within five years [16]. Patients with recurrent disease report a significant impact on their overall quality of life compared to that of women without recurrence, including daily pain, increased emotional burden, activity limitations, and issues concentrating [26]. A single institution cohort study of advanced or recurrent EOC patients receiving CRS and HIPEC was analyzed to identify patterns of recurrence (pelvic, upper abdominal, or extraperitoneal) and whether there exists an association between location of recurrence and patient survival [27]. Results revealed half of the patients analyzed had recurrence outside the peritoneal cavity after HIPEC following CRS. Recurrence location did not impact PFS or OS in HIPEC patients. As HIPEC in ovarian cancer therapy

specifically targets the peritoneal cavity, this pattern of spread suggests that HIPEC maintains local control of EOC and may reduce recurrence within the peritoneal cavity [27].

Skepticism surrounds HIPEC as it is perceived to be highly toxic, causing complications [28]. Current HIPEC trials have not reported any adverse effects yet further analysis into patient quality of life post-HIPEC is necessary for the continuation of HIPEC as a safe therapeutic. In a phase-III randomized trial, patients diagnosed with advanced-stage EOC were assessed for any alterations in their health-related quality of life after CRS with and without HIPEC [29]. The study followed patients from before randomization into the trial through 12 months post-treatment including analysis after several rounds of adjuvant chemotherapy. Patient health-related quality of life was assessed via questionnaires at various time points. In patients receiving HIPEC during CRS, no impairment in health-related quality of life was observed. A secondary analysis of PFS and OS confirmed that HIPEC patients after interval CRS had both an extended PFS and OS, consistent with previous findings [3][12].

In summary, an extension in patient survival and reduction in recurrence rate is evident, yet the mechanistic benefit of HIPEC in advanced EOC remains unknown. Studies are highly supportive of the use of HIPEC in the treatment of advanced EOC and indicate the extension of patient survival (**Table 1**). Based on existing data, the efficacy of HIPEC can be impacted by procedural factors, such as the timing of surgery in the patient's treatment course and the type of chemotherapy utilized. As previously outlined, different chemotherapy regimens may have altered efficacy when used alone vs in combination with other agents. Similarly, platinum sensitivity is a patient-related factor that affects the utility of HIPEC therapy. Molecular tumor-related factors, including deficiencies in homologous recombination and BRCA status, further influence how patients respond to HIPEC therapy. Additional research evaluating the mechanistic benefits of HIPEC is warranted.

2.2. Additional Applications/Future Directions of HIPEC Therapy

A critical factor in deciding patient eligibility for HIPEC treatment is the presence of peritoneal metastases (PM), which is common among ovarian cancer patients. Pressurized Intraperitoneal Aerosol Chemotherapy (PIPAC) is considered a safe localized treatment for PM. PIPAC is an alternative method of intraperitoneal drug delivery via aerosolized drugs. A prospective PIPAC study enrolled 110 PM patients, 14 of which had a primary ovarian diagnosis, and administered several rounds of PIPAC with or without palliative chemotherapy and bidirectional treatment [30]. The Peritoneal Regression Grading score (PRGS) was utilized to investigate histological treatment response to PIPAC, with a primary outcome of complete or major histological response from three treatments. PIPAC with oxaliplatin or cisplatin and doxorubicin confirmed the primary outcome, PIPAC induced a major or complete histological response, a result independent of patient survival. Quality of life declined post-PIPAC with significantly worsened global health scores despite improvement in fatigue, nausea, constipation, and appetite. PIPAC is known to enhance postoperative pain, yet it cannot be concluded that exacerbated pain is the source of the decline in global health scores [30][31]. PIPAC efficacy warrants additional evaluation for use in primary ovarian cancer patients.

Malignancy is highly reported in primary ovarian cancer patients with a common complication of ascites. Continuous hyperthermic intraperitoneal perfusion chemotherapy (CHIPC) is thought to be advantageous over HIPEC due to the combination of hyperthermia treatment with local chemotherapy via laparoscopic administration [32]. To evaluate CHIPC efficacy in presence of malignant ascites, a 36-patient study was performed, of which 12 patients had primary ovarian cancer [32]. Results reveal successful CHIPC with completely resolved ascites in a majority of patients. No significant adverse effects were reported, and improvement in quality of life was associated with the control of ascites. CHIPC involves the administration of significantly lower doses of chemotherapy compared to systemic treatment, hence the reports of CHIPC being advantageous over HIPEC with respect to the treatment of PM [32].

PIPAC and CHIPC are used as a palliative treatment modality specifically for cancers involving peritoneal metastases. Reports of these therapies being advantageous over HIPEC in cases of primary ovarian cancer with respect to overall survival have yet to be reported.

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