

Direct and indirect anticancer effects of hyperthermic intraperitoneal chemotherapy on peritoneal malignancies (Review)

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Received October 16, 2020; Accepted January 13, 2021

DOI: 10.3892/or.2021.7974

Abstract. The successful application of hyperthermic intraperitoneal chemotherapy (HIPEC) illustrates its antitumor activity against primary malignancies and peritoneal metastases. Although the specific underlying molecular mechanisms remain unclear, increasing evidence suggest that HIPEC directly and indirectly inhibits tumor growth, and prolongs overall survival in both hyperthermic and chemotherapeutic manners. To demonstrate the superiority and limitations of such a therapeutic regimen, the present review focuses on the biological and immunological anticancer mechanisms of HIPEC. In addition, the potential combination of HIPEC with other therapies is discussed, as well as its potential to prolong the overall survival time of patients with peritoneal malignancies.

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1. Introduction

According to statistics, peritoneal metastasis of common malignancies is considered unresectable and poses a great challenge in cancer treatment (1). Previously, traditional intravenous chemotherapy was the recommended option for patients with peritoneal metastasis, the efficacy of which is largely limited by myelotoxicity (2,3). The peritoneal plasma barrier and high interstitial pressure of tumor tissues limit the accumulation of traditional intravenous agents in the peritoneal cavity (4). Several clinical trials have confirmed that intraperitoneal chemotherapy can overcome these limitations and extend patient survival time (5). Intraperitoneal drug delivery under hyperthermia conditions, a procedure known as hyperthermic intraperitoneal chemotherapy (HIPEC), has proven to be a more effective interventional therapy for metastatic tumors of the abdominal cavity (6,7). Since the standard nomenclature for HIPEC was devised at the Fourth International Workshop on Peritoneal Surface Malignancy in 2004 (8), its clinical application has drawn great interest. However, as demonstrated in the PRODIGE7 (9) and PROPHYLOCHIP (10) trials, adjuvant HIPEC does not appear to significantly improve patient survival. As an adjuvant therapeutic method, the underlying molecular mechanisms of HIPEC remain largely unknown, which may affect its clinical application. The present review focuses on the direct and indirect effects of HIPEC, particularly at the immunological level.

2. Clinical applications of HIPEC

HIPEC is an important adjuvant treatment for malignant tumors, malignant ascites and intraperitoneal metastases, the aim of which is to perfuse chemotherapeutic agents into the abdominal cavity at a constant temperature and for a specific period (7,11). Giovanella *et al* (12) revealed that exposure to temperatures at 42.5–43.0°C has a significantly greater lethal effect on neoplastic cells compared with non-neoplastic human cells. There are two clinical methods of HIPEC application, namely the open-abdomen and closed-abdomen techniques (13). The open method is usually performed in the operating room directly after surgery and has exhibited significant heat loss in porcine models (14). A meta-analysis revealed

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Key words: hyperthermic intraperitoneal chemotherapy, DNA damage, heat shock proteins, cGAS-STING pathway

that closed HIPEC is used more frequently than the open method, and that the choice of HIPEC method has no impact on the overall recurrence-free survival rate of patients, though this finding requires further verification (15). CO₂-HIPEC is a recently developed technology that promises improved heat delivery into the 'closed' abdomen (14). The closed CO₂-HIPEC system (PRS-1.0 Combat) uses a CO₂ recirculation system to distribute the perfusate and increase pressure within the peritoneal cavity, ensuring intra-abdominal thermal homogeneity, in addition to optimal solution distribution and drug penetration (16). Pressurized Intraperitoneal Aerosol Chemotherapy (PIPAC) employs the CO₂ recirculation method, using a PIPAC micropump to nebulize the liquid cytotoxic drug into droplets of ~25- μ m, generating a polydisperse aerosol in the abdominal cavity that is more effectively absorbed (17,18).

HIPEC has been used to treat colorectal cancer (10,19,20), gastric cancer (21,22), ovarian cancer (7,23), appendiceal neoplasms (24) and other peritoneal metastatic carcinomas (25). van Driel *et al* (7) discovered that among patients with stage III epithelial ovarian cancer undergoing interval debulking surgery, the median overall survival (OS) time of the intravenous- and IP-therapy groups was 49.7 and 65.6 months, respectively (P=0.03). However, in 2003, Verwaal *et al* (19) reported the results of a randomized trial, suggesting that cytoreduction and HIPEC improve the survival times of patients with peritoneal carcinomatosis of colorectal origin. In the 2019 COLOPEC randomized multi-center trial, Klaver *et al* (20) indicated that adjuvant HIPEC did not improve the peritoneal metastasis-free survival times of patients with T4 or perforated colon cancer 18 months post-treatment. In addition, the PRODIGE 7 trial was unable to demonstrate improved OS or relapse-free survival time in patients with peritoneal metastases of colorectal cancer who had accepted oxaliplatin-HIPEC treatment following cytoreductive surgery (CRS) (9). In the PRODIGE 7 trial, median OS time in the HIPEC and CRS-only arms was 41.7 and 41.2 months, respectively. In addition, the rate of grade ≥ 3 complications in the HIPEC arm was higher compared with the non-HIPEC arm (24 vs. 14%) at 60 days. The PROPHYLOCHIP-PRODIGE15 trial also revealed that adjuvant oxaliplatin-HIPEC did not improve patient disease-free survival time compared with standard surveillance in 2020 (10).

The clinical effects of HIPEC remain a contradiction. Although HIPEC has been demonstrated to increase intraperitoneal hydrostatic pressure to enhance drug delivery to the peritoneal surface, and theoretically, to eliminate residual microscopic peritoneal disease, the practice remains controversial (26,27). Thus, investigations on the basic molecular mechanisms of HIPEC may prove beneficial. HIPEC is also known to exert direct and indirect antitumor effects by promoting albuminous degeneration, inducing apoptosis and inhibiting angiogenesis, which may indicate a synergistic effect between hyperthermia and chemotherapy (28,29).

3. Direct hyperthermic injury to tumor cells

Cell membrane and cytoskeleton. During hyperthermia, supranormal temperatures can induce a distinct decrease in membrane and cytoplasmatic proteins, resulting in tumor cell death (30,31). For example, multidrug resistance-associated

protein 1 and 3 are responsible for the failure of several oncological treatments, such as chemotherapy of taxanes, vinca alkaloids and anthracyclines, while the expression of these proteins can be reduced by hyperthermia (32). The expression levels of membrane-bound cytoskeletal proteins, such as actin, are also reduced by hyperthermia, which results in the subsequent loss of integrin CD11a (also known as leukocyte function-associated antigen-1) from the cell surface (33,34). CD11a deficiency or blockade subsequently abrogates the aggregation of Treg cells, enhancing the efficacy of anti-cancer treatments (35). Furthermore, defects in the tumor cell membrane result in enhanced membrane fluidity (36). As a result, hyperthermia-induced membrane remodeling and the release of lipid signals can upregulate cellular thermosensitivity (37). In addition, activation of the purinergic receptor, P2X7, can be potentiated by the associated changes in membrane fluidity, which ultimately promotes tumor cell death (38). Apoptosis is one of the mechanisms underlying hyperthermia-associated cell death, which occurs alongside downregulation of p53 and Bcl-2 expression, as well as upregulation of Bax expression and mitotic catastrophe (39,40).

DNA damage. Early trials have reported that hyperthermia can result in nuclear DNA double-strand breaks (DSBs), single strand breaks and chromosomal aberrations in tumor cells (41,42). Through the enhancement of ataxia-telangiectasia mutated protein (ATM) kinase activity, and an increase in cellular ATM autophosphorylation, foci formation of phosphorylated H2AX (at serine 139; γ -H2AX) can be induced by hyperthermia, which acts as a specific indicator for the occurrence of DNA DSBs (43,44). While DSBs are primarily repaired via non-homologous end joining, hyperthermia increases the probability of incorrect DSB reconnections (45). However, hyperthermia appears to delay the repair of DNA DSBs caused by cisplatin, doxorubicin or radiotherapy, rather than by direct proteasomal DNA damage (46,47). Mild hyperthermia (41.0-42.5°C) has also been reported to induce BRCA2 degradation and inhibit homologous recombination, thus impeding DNA damage repair (41,48). Cisplatin-induced adduct formation is also increased *in vivo*, which is an important determinant of toxicity (49).

4. Indirect effects of hyperthermia

Enhancement of chemotherapeutic effects. In 1994, researchers determined that hyperthermia enhances the effects of intraperitoneal chemotherapy by increasing the uptake of chemotherapeutic agents (50). As a result, the clinically effective dose could be reduced to decrease the incidence of severe side effects (51). Hyperthermia has been demonstrated to enhance the sensitivity of tumors to chemotherapy by the impairing DNA repair (39), and to decrease the number of proliferating tumor cells when combined with chemotherapeutic drugs (52). However, Cesna *et al* (28) suggested that without cisplatin, hyperthermia does not synergistically effect cancer cell viability, indicating that the interaction between chemotherapy and hyperthermia requires further investigation.

Modulation of inflammation and the immune response. Due to the clinical similarity between exogenously induced

hyperthermia and natural fever, it has been speculated that immune cells, including antigen presenting cells (APCs) and natural killer (NK) cells, can be stimulated by hyperthermia to enhance the antitumor effects of chemotherapeutic agents in the abdominal cavity (53). The premise of these immunological influences is that peptides released from dead tumor cells can be internalized by APCs, including dendritic cells (DCs) and macrophages, which subsequently activate cytotoxic T lymphocytes (CTLs) (54,55). In this regard, hyperthermia can substantially enhance the phagocytic potential of DCs and increase DC infiltration by regulating the (C-C) receptor (CCR)7-(C-X-C motif) ligand 21 axis (56). The viability of NK cells is substantially reduced between 41-42°C, while thermal stress activates NK cell cytotoxicity by activating receptor NKG2D and its ligand, MHC class I-related chain A (57).

The peritoneum is a visceral tissue with unique immune functions, in which the largest cell fraction are the peritoneum mesothelial cells (HPMCs) (58). The HPMCs comprise fibroblasts, endothelial cells, macrophages and lymphocytes (59). Tumor-associated macrophages are the primary immune cell population in the tumor peritoneal cavity and can be stimulated to differentiate into two distinct subtypes: Anti-tumorigenic M1 macrophages and pro-tumorigenic M2 macrophages, of which M2 macrophages represent the majority (60,61). M2 macrophages inactivate CD8⁺ T cells through increased expression of programmed cell death 1 ligand 1 and cytotoxic T lymphocyte antigen 4 (62). In addition, M2 macrophages accelerate tumor cell proliferation through signal transducer and activator of transcription 3 (STAT3) activation via transforming growth factor β (TGF- β), interleukin (IL)-6 and IL-10 (63,65).

A study suggested that fever-like mild heat (~43°C) can synergistically induce macrophage polarization from the M2 to M1 phenotype during low-temperature photothermal therapy with a lipid nanocomposite (66). However, to the best of our knowledge, no studies have reported changes in the immunological competency of the peritoneum in patients undergoing HIPEC, which may indicate a determining factor for HIPEC resistance, and thus requires further investigation. In addition, hyperthermia may impair the functions and decrease the number of immune cells (67,68), thus future studies should also focus on the dual effects of hyperthermia.

Fever is commonly considered to be a protective response following inflammation (69). Artificial HIPEC-induced fever appears to evoke an inflammatory response with the release of cytokines, such as IL-1, IL-6 and TGF- β (70). IL-1 is expressed by malignant and infiltrating cell, and promotes tumor progression and invasiveness (71). By activating STAT3, classical IL-6 signaling blocks DC maturation, inhibits T-cell activation and enhances tumor cell proliferation (72). In addition, IL-6 and TGF- β are considered to promote the differentiation of Th17 cells, which support tumor progression by secreting immunosuppressive IL-17, thus facilitating immune escape (73). Conflictingly, hyperthermia phospho-regulates gp130, which is anchored to the endothelial cell membrane of tumor microvessels (74). Soluble IL-6 receptor α binds IL-6 and gp130 to activate IL-6 trans-signaling, which regulates high endothelial venule adhesion and promotes the trafficking and recruitment of CD8⁺ T cell into the tumor site (75).

Regulation of the heat shock response. The expression of molecular chaperone heat-shock proteins (HSPs) in the abdominal cavity (including HSP-70, HSP-72 and HSP-92) can be upregulated by hyperthermic antineoplastic agents, which protect the organs from heat-induced stress (76). Similar to other multidomain proteins, HSPs recognize and bind unfolded/disordered sequences to facilitate the folding/refolding of these sequences, or simply to present themselves to the proteasome for destruction, protecting intracellular proteins from stress-induced cellular damage (77,78). The upregulation of HSP machinery in cancerous cells may prevent the misfolding and degradation of mutated and overexpressed oncoproteins (79). The highly conserved molecular mechanisms of HSPs hinder the antiproliferative and apoptotic effects of HIPEC on tumor cells (80). For example, upregulation of HSP27 resulting from HIPEC/CRS combination treatment may promote thermotolerance and chemoresistance (81). However, chemotherapy can also suppress HSP27 expression, rendering cancer cells sensitive to mild hyperthermia (43°C) (82).

Zunion *et al* (82) have suggested that following HIPEC, HSP90 induces an anticancer immune response at the cell surface. As with the HSP90 inhibitor, 17-allylamino geldanamycin, hyperthermia causes drugs to accumulate in the tumor, leading to potent antitumor activity (83). The increased delivery of HSP-targeted chemotherapeutics can be attributed to the hyperthermia-induced expression of cell surface HSP glucose regulated protein 78 kDa, which targets N-(2-hydroxypropyl) methacrylamide copolymer-drug conjugates (84).

Professional APCs of the innate immune response can be stimulated by extracellular HSPs, followed by cytokine release and the expression of cell surface molecules (85). In addition, acting as a tumor vaccine, the cross-presentation of HSP-bound peptide antigens to MHC class I molecules can stimulate adaptive immunity via DCs (86,87), leading to the efficient induction of antigen-specific CTLs (88,89). There is also evidence that macrophages can be activated by heat shock factor-1 through upregulation of the inducible nitric oxide synthase gene (90).

5. Role of chemotherapy in HIPEC

Pharmacokinetics of chemotherapeutics in the peritoneal cavity. The peritoneal cavity is a closed space that consists of the peritoneum, abdominal organs and 50-70 ml peritoneal fluid (91). The peritoneum is an extensive serosal exchange membrane comprised of a single layer of squamous HPMCs (~25 μ m in diameter), collagen, adipose tissue, lymphocytes, blood vessels and lymphatics (4). The so-called peritoneal-plasma barrier comprises HPMCs, the subserosal interstitium and the capillary walls (92). As the primary absorption barrier, large molecular drugs in the peritoneal cavity are absorbed slowly into the systemic blood circulation (93). The area under the concentration-time curve (AUC) of drugs from the peritoneal cavity to the plasma demonstrated the pharmacological advantage of intraperitoneal administration (94).

Table I outlines the pharmacokinetic properties of commonly used chemotherapeutics following intraperitoneal administration (95-101). As presented in Table I, a high peritoneal AUC

Table I. Pharmacokinetic characteristics of commonly used chemotherapeutics following hyperthermic intraperitoneal chemotherapy administration.

Drug	Molecular weight, Daltons	Intraperitoneal Dose, mg/m ²	Carrier solvents	Mean AUC, peritoneal	Mean AUC, plasma	AUC ratio	Drug penetration distance	Refs.
Mitomycin C	334.3	35.0	Dialysis fluid	630±130, mg • min/l	71±24, mg • min/l	10.10±4.60	<5 mm	(94)
Cisplatin	300.1	50.0	Dialysis fluid	2.87±0.52, mM • min	0.46±0.05, mM • min	6.28	1-3 mm	(95)
Oxaliplatin	397.3	460.0	5% Dextrose	2,412.9±711.4, mg • min/l	138.1±33.1, mg • min/l	18.60	1-2 mm	(96)
Paclitaxel	853.9	175.0	Normal saline	736.8±305.2, mg • h/l	2.284±1.185, mg • h/l	387.00±260.00	80 cell layers	(97)
Docetaxel	861.9	75.0	Normal saline	85.10, mg • h/l	0.7634, mg • h/l	207.40	NA	(98)
Mitoxantrone	517.4	28.0	Normal saline	15,530±2,471, ng • h/l	1,036±394, ng • h/l	12.50	5-6 cell layers	(99)
Doxorubicin	543.5	60.0-75.0	Normal saline	372.0±260.0, mg • min/l	4.1±6.0, mg • min/l	162.00 ±113.00	4-6 cell layers	(100)

AUC, area under the concentration-time curve; NA, not available.

reflects high local exposure and potential drug efficacy, while a low plasma AUC indicates low systemic exposure and reduced systemic toxicity (102). The dose of the drug used in HIPEC is another factor affecting intraperitoneal administration (103). There are usually two primary methods of dose determination, including body surface area-based and concentration-based dose calculations (104). Lemoine *et al* (105) compared these methods using oxaliplatin-based HIPEC and found no differences in pharmacokinetic advantage between the two models. Concentration-based dose determination appeared to result in a higher drug concentration in the tumor nodule, whilst imparting higher toxicity and efficacy (106). However, due to compromised lymphatic function, leaky vasculature and the dense structure of the extracellular matrix, the penetration depth of these drugs into the tumor nodule was limited to several millimeters (100). Previous studies have suggested that the combination of antiangiogenic therapy and intraperitoneal chemotherapy improves drug penetration by decreasing interstitial fluid pressure (107-109). Drugs with nano-sized particles, such as paclitaxel, have also been used in intraperitoneal chemotherapy to increase exposure time in the peritoneal cavity, and thus improve intratumoral drug accumulation (110). It is well-known that CO₂-HIPEC enhances drug penetration in the tumor (18). Shamsi *et al* (111) reported a novel magnetically assisted strategy, using drug-coated magnetic nanoparticles and a permanent external magnet to increase the final concentration in tumor nodules (radius, 5-10 mm).

As for the selection of intraperitoneal chemotherapeutics for solid tumors, several factors must be considered in addition to the selection of effective proliferation inhibitors, such as the active form and half-life of agents (112). The effects of peritoneal delivery are based on direct contact between tumor cells and the chemotherapeutic agent (113). As these agents must be delivered in an active form, chemotherapeutics that require activation by hepatic metabolism are considered unsuitable (113).

Immunological effects of chemotherapy. Increasing evidence suggest that several immunological factors can be induced by conventional chemotherapeutic agents, including the composition, phenotype and function of immune cells, as well as alterations in several immune-related parameters (114,115). For example, Latchman *et al* (116) revealed that the expression of T cell inhibitory molecule programmed death receptor-ligand 2 (PD-L2) on both human DCs and tumor cells is markedly decreased following exposure to platinum-based chemotherapeutics. As a second ligand for PD-1, PD-L2 inhibits T cell activation (117). In addition, Treg cells and circulating myeloid-derived suppressor cells have been demonstrated to be depleted by paclitaxel, gemcitabine and vinorelbine, therapeutically enabling relevant tumor-targeting immune responses (118-120). As for the immunological effects of chemotherapeutics, immune effector cells may be stimulated, and Treg cells may be depleted following the release of cytokines and chemokines, while tumor-specific antigens containing tumor cell peptides may be internalized by APCs following chemotherapeutic exposure (121).

Chemotherapy-induced immunological cell death (ICD) (Fig. 1) may enhance the immunological effects of treatment (122,123). Following hyperthermia- and

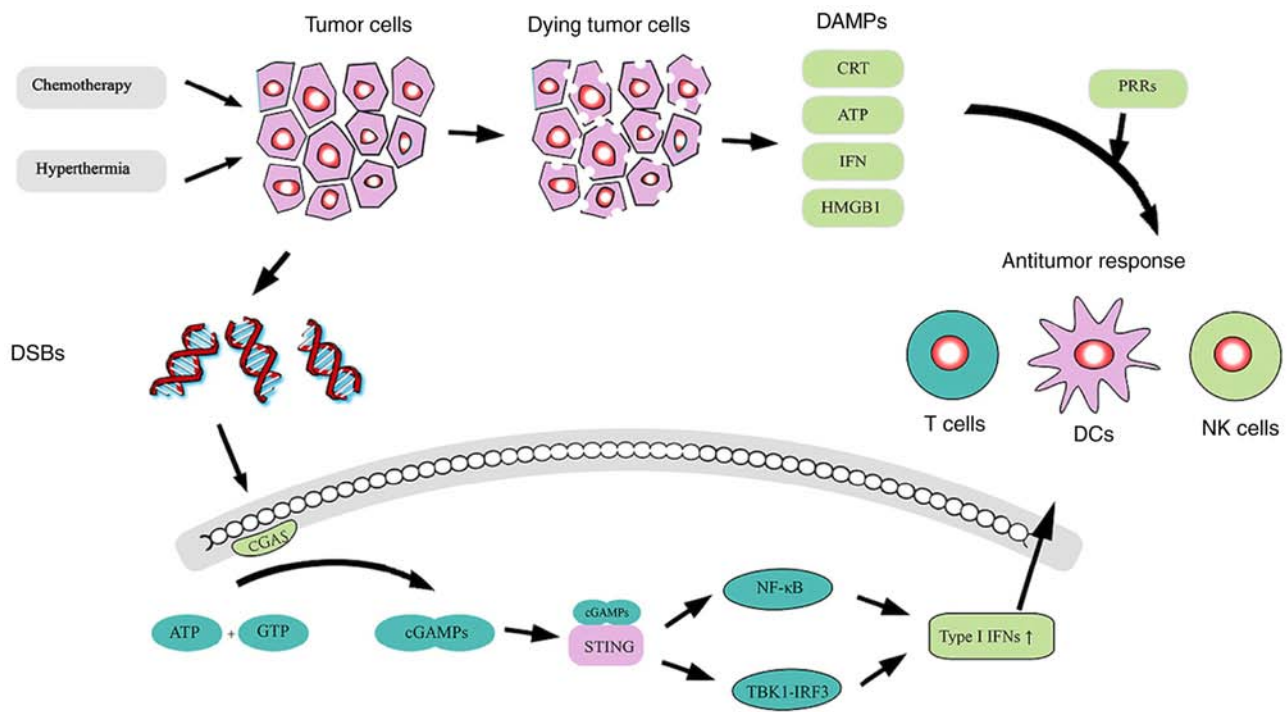


Figure 1. Immunological cell death and the CGAS-cGAMP-STING pathway are activated by hyperthermic intraperitoneal chemotherapy. Following hyperthermia and chemotherapeutic suppression, DAMPs are released from dying tumor cells. By binding to PRRs, DAMPs can elicit innate and/or adaptive immune responses. DNA released from tumor cells can enhance antitumor immune responses via the cGAS-cGAMP-STING pathway. Downstream non-canonical NF- κ B and TBK1-IRF3 pathways are subsequently activated to induce the expressions of type I IFNs, which initiate innate and adaptive immune responses. CGAS, cyclic GMP-AMP synthase; cGAMP, cyclic GMP-AMP; STING, stimulator of interferon genes; DAMP, damage-associated molecular pattern; PRR, pattern recognition receptors; IRF, interferon regulatory factor; IFN, interferon; DSBs, DNA double-strand breaks; NF, nuclear factor; DC, dendritic cell; NK, natural killer.

chemotherapy-associated tumor cell death, damage-associated molecular patterns (DAMPs) are released, which include surface-exposed calreticulin, secreted ATP and IFN, and high-mobility group protein B1 (130). By binding to pattern recognition receptors, DAMPs can elicit innate and/or adaptive immune responses (124). During anticancer immune responses, primary effector cells, such as DCs, internalize tumor-associated antigens and mature in the surrounding tumor tissues, resulting in the production of immune-activating cytokines (125). T cells are then recruited, which destroy tumor cells. Notably, this phenomenon was not observed in immunodeficient mice (126). Accordingly, CTLs are one of the most effective means to combat chemotherapeutic resistance, serving a key role in cancer treatment (54). Thus, it was hypothesized that this 'passive immunotherapy' may be an important adjunct strategy for overcoming chemotherapeutic resistance (127). In addition, clarifying the molecular mechanisms of ICD and applying them to the development of a cancer-specific vaccines during HIPEC can potentially improve chemotherapeutic resistance and eliminate residual tumor cells (122).

Cyclic GMP-AMP synthase (cGAS)-cyclic GMP-AMP (cGAMP)-stimulator of interferon genes (STING) pathway during HIPEC. During chemotherapy-induced tumor cell death, the release of DNA, a tumor-specific antigen, can enhance antitumor immune responses via the cGAS-cGAMP-STING pathway (Fig. 1). The production of cGAMP can be catalyzed by the interaction between dsDNA and cGAS, after which

cGAMP activates the adaptor protein STING, a second messenger in APCs (128,129). The downstream NF- κ B and TBK1-IRF3 pathways are then activated to induce the expression of type I IFNs, which induce innate and adaptive immune responses, including various immune cell subsets, such as NK cells, DCs, B cells and effector T cells (130,131). As hyperthermia can promote tumor cell DNA damage (43,44) and delay the repair of DSBs caused by chemotherapy (48,49), it may be a sensitizer for such a process. Thus, HIPEC may exert unexpected antitumor effects following activation of the CGAS-cGAMP-STING pathway.

6. Conclusions

Following improvements by medical personnel, HIPEC appears to increase the OS rate of patients more favorably with peritoneal metastatic carcinoma compared with systemic chemotherapy. However, the therapeutic effects of HIPEC have been debated since the publication of the PRODIGE7 and PROPHYLOCHIP trial results. Thus, additional clinical trials are required to definitively establish the role of HIPEC in abdominal metastatic adenocarcinoma.

HIPEC exhibits several noteworthy side effects, such as visceral hemorrhage, fatigue and gastrointestinal or neurotoxic effects (132,133). Intra-abdominal infection, peritoneal recurrence and small bowel obstruction are also frequently observed (134). Antibiotic-induced intestinal dysbiosis can result in the failure of cancer immunotherapy (135). Thus, detrimental changes in the gut microbiome of patients undergoing

HIPEC may also occur (136,137). It was hypothesized that temperate chemotherapy delivered into the abdominal cavity may also lead to intestinal dysbiosis; however, further clarification is required.

The present review focuses on the dual actions of chemotherapeutic drugs and hyperthermia using HIPEC to clarify the molecular mechanisms underlying the enhanced efficacy of HIPEC, and to identify other therapies for its combinatory use. However, the precise molecular indexes, not just the retrospective indexes, require further investigation to predict patient prognosis.

Acknowledgements

Not applicable.

Funding

The present review was financially supported by the National Natural Science Foundation of China (grant nos. 31700792 and 81801568) and the Maternal and Child Health Association Foundation of Jiangsu (grant no. FYX202017).

Availability of data and materials

Not applicable.

Authors' contributions

YZ and YW performed the literature review and drafted the initial manuscript. JW and CW revised the manuscript for important intellectual content and confirmed the authenticity of all the raw data. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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