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Peritoneal carcinomatosis: Effectiveness and Limitation of the Treatment

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Abstract:

Primary peritoneal cancer (PPC) was first portrayed by Swerdlow M. in 1959. It is an idiopathic cancer that develops in the abdominal cavity's peritoneal layers. With its identical histology to the primary epithelial ovarian carcinoma, their behaviors are similar. Due to it frequently being diagnosed late and its ambiguous clinical manifestation, PPC has a very low survival rate; it is considered a stage III or IV cancer. Currently, standard treatments include intraperitoneal chemotherapy and surgical resection with locoregional control of the disease. Many other treatments are available and will be mentioned later in this review, however, most are adapted from remedies of other cancers due to the lack of research interest in PPC. There is potential in combining targeted therapies with chemotherapy; several reports suggest that this method has improved the prognosis of choroid plexus carcinoma (CPC) quite substantially. Regardless, much more research has to be done to provide advanced and conclusive evidence.

Keywords **—Choroid plexus carcinoma, monoclonal antibodies, primary peritoneal cancer**

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I. INTRODUCTION

Primary peritoneal cancer (PPC), also called peritoneal surface malignancy, was an extraovarian primary peritoneal carcinoma (EOPPC) as described as "Mesothelioma of pelvic peritoneum" (1, 2). This rare cancer originates in the mesothelium of the abdomen, spreads extensively throughout the serous membrane lining of the peritoneal cavity (consists of the viscera, coelom in amniotes, and abdominal cavity) (3). It usually includes the omentum, but not the ovaries; its behavior is similar to serous ovarian cancer due to its identical histology with the primary epithelial ovarian carcinoma (3, 4). Classifications had been made based upon histology, including EOPPC, serous surface papillary carcinoma, papillary serous carcinoma of the peritoneum, extra ovarian Mullerian adenocarcinoma, and normal-sized ovarian carcinoma syndrome as different types of primary peritoneal cancer, whereas malignant mesothelioma (MPM), multicystic mesothelioma, leiomyosarcomas, leiomyomatosisperitonealisdisseminata, and desmoplastic small round cells tumor (DSRCT) as types of secondary peritoneal cancer—whereby malignant cells metastasize to the peritoneal cavity from other sites (1, 5, 6).

PPC is considered stage III or IV, while secondary peritoneal cancer is stage IV; late diagnosis stems from vague clinical manifestations, resulting in a low survival rate (7). Standard treatments include intraperitoneal chemotherapy and surgical resection with locoregional control of the disease (if the disease is not extensively systemic) (8). This review aims to explore

peritoneal cancer (PC) in terms of its etiology and epidemiology in hopes of spreading awareness to allow for better treatments in the future.

II. ETIOLOGY AND EPIDEMIOLOGY

PPC is an idiopathic cancer that develops in the abdominal cavity's peritoneal layers. Its subtype, EOPPC, is similar to serous ovarian carcinoma, but only affects females (mean age of 56-62 years). It is reported to develop in only a few males (9, 10). In 17.6% of cases, germline mutations in the BRCA 1 gene are its cause (10). Thus, serous peritoneal cancer should be ruled out in any patient with familial breast cancer. In contrast, asbestos exposure is the cause of approximately 33% to 50% of malignant peritoneal mesothelioma cases, which is a malignant tumor that typically affects older males (60 years and older) (11).

In postmenopausal women, there is a correlation between elevated estrogenic state and disseminated peritoneal leiomyomatosis—a secondary tumor occurring in conjunction with retinoblastoma in Li Fraumeni syndrome. Adolescents (median age 19 years) and Caucasians account for 85% of DSRCT cases, which is caused by the translocation of [t(11;22)(p13;q12)] (12-14). Secondary peritoneal carcinoma is frequently caused by malignant cells invading the stomach, colon, pancreas, gallbladder, appendix, breast, uterus, ovary, or lung tumors. Pseudomyxoma peritonei (PMP) is used to describe peritoneal involvement in appendiceal cancer, which when effectively managed, eliminates recurrence for life. Metastasis from ovarian, gastric, or colorectal cancers is linked with higher risks of mortality and relapse, which makes them the most prominent causes of metastasis into the peritoneal linings (9).

The prognosis of PC is generally poor; the survival rate of PPC ranges from 11 to 17 months, negatively correlating to the stage of cancer for secondary peritoneal cancer (5 to 10 months for stages 0 to II, and 2 to 3.9 months for stages III and IV) (15, 16). PPC's age-standardized incidence rate is 6.78 per million, reflecting its nature as uncommon and advanced in humans (17, 18). It is most frequently spotted among the white population and least amongst the blacks. Serous carcinoma of the peritoneum makes up 10% of pelvis cancers; unlike the greatly fatal and least common peritoneal cancer, malignant mesothelioma, it represents the most histologically common type of PPC (2, 9). The highest number of PC cases are of pleural mesothelioma (10% of cases), followed by MPM (15% of cases) (6).

In the peritoneal cavity, peritoneal metastasis is the most prevalent malignant transformation: present in 75% of ovarian cancers during initial presentation, coexisting with the primary tumor in 55% of cases, and 45% of non-gynecological malignancies during follow-up (19, 20). Moreover, during the time of diagnosis, it is associated with 5 to 10% of colorectal tumors cases and found in 14% of gastric cancer cases (5). In 9% of cases, peritoneal dissemination is a result of extra-abdominal malignancies rather than the viscera of the peritoneal cavity—40.8%, 25.6%, and 9.3% from the breast, lung, and melanoma, respectively (6, 15, 20).

III. TREATMENT FOR PRIMARY PERITONEAL CANCER

There are several regimens for treating PPC that are greatly similar to the treatment of epithelial ovarian cancer; including surgery, chemotherapy, targeted therapy, hormonal therapy, and radiotherapy (21). PPC is initially treated surgically. The following are the various types of surgery: 1) Removal of the uterus, ovaries, and fallopian tubes (total hysterectomy and bilateral salpingo-oophorectomy) 2) omentectomy; and 3) surgical debulking (3, 22-24). Chemotherapy is used to treat peritoneal carcinomatosis in its early stages. Post-surgery, chemotherapeutic drugs are used, such as *carboplatin* (*Paraplatin*,*Paraplatin AQ)* or *cisplatin* and *paclitaxel* (*Taxol*) or *docetaxel* following surgery (*Taxotere*). *Carboplatin* and *paclitaxel* are the most frequently used chemotherapy agents. Additionally, *etoposide* (*Vepesid, VP-16*), *gemcitabine* (*Gemzar*), *topotecan* (*Hycamtin*), *vinorelbine* (*Navelbine*), and *pegylated liposomal doxorubicin* may be used if cancer recurs (*Caelyx*) (25, 26). Instead of intravenous chemotherapy, intraperitoneal chemotherapy may be used (27). It may be offered to women who have small residual

tumors (less than 1 cm in diameter) following surgical debulking (28). Occasionally, chemotherapy is administered prior to debulking surgery. If cancer shrinks due to chemotherapy, surgery can be used to remove the remaining cancer. Following the surgery, additional chemotherapy is administered. This procedure is referred to as interval debulking surgery. Patients with certain advanced PPCs may be given targeted therapy, on some occasions, in conjunction with a chemotherapy drug (29).

Bevacizumab (Avastin), Olaparib (Lynparza) for women with a BRCA1 or BRCA2 gene mutation, and *Niraparib* are all examples of targeted therapy drugs (*Zejula*) (30). After receiving platinum-based chemotherapy with *carboplatin* or *cisplatin*, *Olaparib* or *Niraparib* may be used as maintenance therapy in women who have recurrent PPC (31). In addition to chemotherapy, hormonal treatment may be given to treat advanced PPC (32, 33). Hormonal therapy options include Arimidex, *Femara*, and *Tamoxifen* (*Nolvadex*, *Tamoxifen*) (34). The use of radiation therapy in treating advanced PPC is basically for an advanced stage of PPC (35, 36).

IV. NEOADJUVANT BIDIRECTIONAL CHEMOTHERAPY

There are four different points in the timeline for intervention when it comes to the practical application of chemotherapy in PC patients (37). Neoadjuvant bidirectional chemotherapy is administered via both intraperitoneal and intravenous methods. It has been considered to potentially reduce the size of tiny PC nodules. In theory, it may assist curative cytoreductive surgery (CRS) if PC is revealed in exploratory laparoscopy. Numerous organizations have documented radiological and clinical responses (38). Although this method may lower the tumor load that must be treated during CRS, there are various drawbacks (39). The proper distribution of intraperitoneal medication may be obstructed by adhesions from previous surgeries (40). Due to the rarity of complete responses, more cytoreduction-chemotherapy is required to reach the therapeutic goal (41). Research shows that neoadjuvant intraperitoneal chemotherapy increases the morbidity and mortality associated with subsequent surgical treatment; extensive fibrosis may ensue as a side effect of chemotherapy, which makes it challenging, if not, unattainable to assess the extent of PC (42, 43).

V. TREATMENT OUTCOME

PC patients tend to receive neoadjuvant treatment. It was found to be equivalent to upfront debulking advanced ovarian cancer patients within two randomized trials (29, 44). However, post-surgery survival rates in the trials were lower than anticipated by gynecologic oncologists, and results have been challenged. A subsequent Cochrane review reaffirmed that the advantages of this method are unclear (45). In an analysis of neoadjuvant chemotherapy-treated PPC or ovarian cancer patients, an outstandingly unsatisfactory survival is shown, even though PC patients had a higher rate of complete surgical debulking following neoadjuvant chemotherapy (46). Although this is one of the most extensive studies to date, the size of the cohort precludes additional subgroup investigations such as survival comparisons between patients who receive the same treatment. Moreover, due to the possible existence of significant patient selection biases for primary or interval debulking, the design of this cohort study is considered an inadequate determination of neoadjuvant chemotherapy's impacts (47). Emerging research shows that interval debulking following neoadjuvant chemotherapy may pose a higher risk of developing platinum resistance; using chemotherapy to treat large-volume tumors prior to surgery rather than using it to treat microscopic residual disease following initial debulking also contributes to the high possibility of platinum resistance development. Likewise, mounting research demonstrates that the molecular characteristics that preclude adequate cytoreduction may also significantly contribute to treatment resistance. In other solid tumors, such as pancreatic cancer, fibrotic stromal responses are linked to poor drug absorption and primary chemoresistance (48, 49).

A large percentage of peritoneal carcinomas are mesenchymal in origin, which could relate to the

pattern of metastasis. Additional *in vivo* research is essential for a full understanding of the imperative processes underlying the pathogenesis of peritoneal cancer (50). This significant molecular characteristic makes peritoneal tumors less resectable to surgical intervention and more resistant to chemotherapy, which leads to increased fatality. Although constant improvement in survival is not shown, interval debulking following neoadjuvant chemotherapy is a prudent strategy in some cases. Enhancements in CRS and chemotherapy in PPC patients may be done through developing treatment interventions or novel drugs that target either the tumor stroma or pathways involved in stromal activation.

However, no definitive agreement on the optimal technique has been obtained (50). There has been no prospective controlled clinical trials undertaken to date that addresses the superiority of one procedure over another in terms of surgical morbidity, results, and personnel safety (51). Each approach has distinct operational advantages and disadvantages, so future prospective research is required to determine which option is best. The differences in hyperthermic intraperitoneal chemotherapy (HIPEC) delivery are possibly more theoretical than real because data from centers using closed versus open abdomen revealed no comparable difference in survival rates. Today, the optimal technique is frequently utilized and refined at each specialized institution involved in managing peritoneal-surface cancer (48). Death occurs in 15% of patients with PPC and 35% of patients with recurring intraperitoneal PC (solely in the peritoneum). Unlike in patients with secondary PC with a gastric origin, systemic chemotherapy resulted in a rise in median survival for patients with metastatic gastric cancer to 7-10 months (47, 52).

Presently, of those expected for probable curative resections and of all stage II and III patients, 10-20% and 40% are found to have peritoneal seeding at the intraoperative abdominal examination respectively; with postoperative peritoneal recurring in 20-50% of patients following radical surgery. The last 4 decades showed an improvement in the multimodal therapeutic approaches on PC, allowing for an absolute tumor cytoreduction, rather than traditional debulking surgery that often leaves macroscopic residual disease. The combined effects of anticancer with hyperthermia on peritoneal tumor cell lines were investigated by Sugarbaker and team (who found that the origin of PC is low-grade malignancy without the invaded cells, which HIPEC and CRS can treat effectively (52).

VI. LIMITATION OF THE TREATMENT

Platinum medications are highly effective against ovarian cancers and PPC (49, 52). Therefore, it is beneficial to find ways to continue platinum-based therapy in patients who are hypersensitive to platinum (53). The first approach is to make mastocytes desensitized to platinum-based drugs—usually *carboplatin*; patients are exposed to gradually increasing doses of dilute *carboplatin* formulations, which causes desensitization (50). Desensitization is frequently successful: as indicated by a trial, it successfully re-challenged 88% (29 of 33) of clinically proven carboplatin sensitive patients (54). An alternative method of desensitization is to inhibit the immune response with corticosteroids beginning 24 hours before the triggering chemical is used (52). Patients who do not respond to the platinum-based strategies generally switch to a non-platinum procedure; however, the rates of response to them seem to be much lower. A different strategy of treatment for patients with *carboplatin* hypersensitivity is replacing *carboplatin* with *cisplatin* and performing the regimen in the absence of any specific desensitization (54). Although the mechanisms behind hypersensitivity to platinum drugs remain unknown, the platinum components of these compounds are surely not the sole cause of it. Whilst containing platinum combined with two ammonium groups is a common trait between the two, cisplatin and carboplatin have significant distinctions structurally and biologically. The molecular study has revealed that *cisplatin*, *carboplatin*, *oxaliplatin*, and tetraplatin all have markedly different effects on many gene expressions (including several involved in the cell cycle and cell signaling) (52, 54).

The method reported in this research may be possible for epithelial ovarian cancer or PPC patients who were unsuccessful in *carboplatin* desensitization. However, there is still a reported 25% incidence of developing a hypersensitive reaction to the substitute platinum (*cisplatin*) following *carboplatin* hypersensitivity; even worse, two fatal *cisplatin* reactions. This emphasizes the need for informed consent and sufficient anaphylactic facilities.

To predict future carboplatin successfulness, some have suggested skin testing for *carboplatin* sensitivity; a negative result shows high likeliness of attainability, while a positive result is less particular. Twenty-five (66%) of 38 patients with a past *carboplatin* response received a positive result in one trial. Regardless, 37 (99%) completed a *carboplatin* desensitization programme. Positive skin test patients had higher subsequent reactions during desensitization than negative test patients (52). There is inconclusive evidence to determine whether newer platinum compounds like *oxaliplatin* or *nedaplatin* have roles in a preceding *carboplatin* or *cisplatin* response (31). Additional research is required to find the best way to treat a platinum-sensitive patient with severe platinum hypersensitivity (52).

VII. FUTURE DIRECTION

Peritoneal cancer is a late-stage manifestation of various gastrointestinal cancers, including appendiceal, colorectal, and gastric cancer (47, 55). Tumors spread to and settle on the peritoneum of PC patients, frequently leaving patients with no treatment choices other than palliative care (56). The median survival time with colorectal PC is roughly five months; palliative systemic therapy can extend this to around twelve months. However, in some individuals with a low tumor burden, CRS and HIPEC with a curative purpose are achievable. Median survival is as high as 63 months in well-selected individuals following complete CRS (57). For patients to have additional therapy choices, such as CRS/HIPEC, earlier identification of patients at risk of developing or having newly developed PC may help (58). Albeit, imaging abnormalities cause PC to be identified late; frequently, it is identified during invasive procedures such as laparoscopy or laparotomy (59). For enhancements in patient outcomes, it is necessary to design a PC-specific screening approach that is accurate and minimally invasive. An analysis of PC biomarkers circulating in patients' serum can bring about “liquid biopsy”, which can give rise to a more targeted treatment strategy and earlier intervention (51).

Biomarkers for peritoneal carcinoma require more investigation; distinguishing between metastatic peritoneal illness and solid organ metastases ought to be biologically viable and therapeutically beneficial (60). For clinical applications, it will be necessary to build reliable and efficient methodologies and acknowledged standards. Prospective sample collection for retrospective analysis should be a component of future clinical work in this sector (47, 61).

CONCLUSIONS

Currently, the late intervention of PC due to imaging findings and invasive procedures—hinders the outcomes of patients. To progress, an accurate and specific minimally invasive surgery (MIS) to screen PC must come about, alongside employing stable PC biomarkers. Liquid biopsy—biomarkers in serum—has great potential to provide earlier diagnosis and individual treatment programs for patients. Patient-derived exosomes (obtained from several bodily fluids) should be considered a replacement for currently-used volatile biomarkers. It is highly probable for survival rates of PC patients to improve, for liquid biopsy becomes established to treat the symptoms of PC better.

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