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Review Article

Immune reaction by cytoreductive prostatectomy

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Abstract: Prostate cancer (PCa) is the most common non-cutaneous cancer among men and the second leading cause of male cancer deaths in the United States. With no effective cure for advanced disease, the survival rates of castration-resistant disease and metastatic disease remains poor. Treatment via hormonal manipulation, immunotherapy, and chemotherapy remain marginally effective, indicating the need for novel treatment strategies. Cytoreductive prostatectomy (CRP) has grown as a treatment modality for metastatic castration resistant prostate cancer (mCRPC) and an emerging body of literature has demonstrated its survival benefits. In this review, we hope to further explore immunologic changes after CRP and the resultant effects on oncologic outcomes. Conclusively, the data and technical considerations of CRS evolve, CRS may continue to expand treat various type of metastatic cancer. Still, there are little reports about immunological changed after CRP. However, based on technical improvement, CRP and combinational immunotherapy are developing treatments of metastatic disease.

Keywords: Prostate cancer, radical prostatectomy, metastasis, cytoreductive

Introduction

Prostate cancer (PCa) is the most common non-cutaneous cancer among men and the second leading cause of male cancer deaths in the United States [1]. In 2018, it is estimated that 29,430 men will die from PCa. Although radiotherapy and surgery effectively treat localized disease, approximately 30% eventually recur following a definitive therapy. Furthermore, with no effective cure for metastatic disease, the 5-year-survival rate for metastatic PCa is only 29% [1]. In patients with metastatic disease, medical or surgical castration is generally accepted as first-line therapy. Androgen deprivation therapy (ADT) is the cornerstone in the treatment of metastatic PCa, followed by and combined with second-line hormonal treatments such as enzalutamide or abiraterone. However, castration-resistant prostate cancer (CRPC) eventually emerges with a median time of 18-24 months [2-4]. Once CRPC develops, secondary hormonal manipulation, immunotherapy, and chemotherapy are marginally effective and the average life expectancy is approximately 5 years [5, 6].

In 1995, Hellman and Weichselbaum [7] introduced the concept of cytoreductive surgery (CRS) - the resection of the primary tumor or metastases to reduce tumor burden-in oligometastatic cancer. More recently, cytoreductive prostatectomy has been explored in the literature. Satkunasivam et al., using the SEER-Medicare database, identified patients ≥66 years old with metastatic PCa treated with radical prostatectomy, intensity modulated radiation therapy, conformal radiation therapy or no local therapy [8]. On multivariable analysis CRP correlated to a 52% decrease (HR 0.48, 95% CI (0.27-0.85), P=0.001) in cancer-specific mortality (CSM), adjusting for socioeconomics, primary tumor characteristics, comorbidities, ADT, and bone radiation within 6 months of diagnosis. Furthermore, a propensity score adjusted analysis, demonstrated a 45% decrease (HR 0.55, 95% CI 0.30-0.72) in CRP relative to no local therapy (NLT) group. Heidenreich et al. in 2015, showed the benefits of CRS in well selected men with metastatic prostate cancer who respond well to neoadjuvant androgen deprivation therapy [9]. A total 23 patients with biopsy-proven prostate cancer (minimal osse-

ous metastases, absence of visceral or extensive lymph node metastases and PSA decrease to <1.0 ng/ml after neoadjuvant ADT) who underwent CRP were analyzed compared with control group consisted of 38 men who were treated with ADT without local therapy. Median time to castration resistant prostate cancer was 40 months (IQR=9-65) and 29 months (IQR=16-59) in the CRP treatment group and control group, respectively (P=0.04). While overall survival was similar in both groups, patients undergoing CRP experienced significantly better clinical progression-free survival (38.6 vs. 26.5 months, P=0.03) and cancer specific survival rates (95.6% vs. 84.2%, P=0.04). Regarding the safety and feasibility of CRP, Sooriakumaran et al. in 2016, published a series, n=106, with newly diagnosed mPCa who underwent CRS [10]. 79.2% of patients had no complications; separately, positive-margin (53.8%), lymphocele (8.5%), and wound infection (4.7%) rates were observed and the authors concluded that CRP is a safe procedure for many. No differences in perioperative complications were seen in M1b relative to M1a patients. In a study by Gandaglia et al. in 2017 [11], perioperative and long-term oncologic outcomes of CRP was found to have an acceptable safety profile no perioperative mortalities. Leyh-Bannurah et al. in 2017, demonstrated CRP had a strong protective effect on patients with one or less risk factor (Subhazard ratio (SHR) 0.16, 95% CI, 0.09-0.28) [12]. In patients with two or more risks, this protective effect reduced but CRP was still effective at decreasing CSM relative to patients with NLT control group (SHR 0.6). In 2017, multicentric prospective data from the Local Treatment of Metastatic Prostate Cancer (LoMP) Trial has also been published [13]. The patients who had at least one histologically confirmed metastatic lesion, excluding pelvic lymphadenopathy were selected. CRP was performed in asymptomatic patients, with resectable primary tumor (n=17). Surgical complications within 3 months postoperatively were analyzed compared with patients who got only standard of care (n=29). In 23.5% of CRP patients, PSA was sustained without death or development of castrate resistance and 44.8% of patients in the NLT, or standard of care group, became castrate resistant and 24.1% of patients died. There was a significant survival benefit for patients undergoing CRP (2-yr OS 100% vs. 55% and 2-yr CSS 100% vs. 61%).

Metastatic prostate cancer immunotherapy

PROSTVAC

PSA-TRICOM (PROSTVAC) is a poxvirus-based peptide vaccine encoding PSA and B7.1, ICAM-1, and LFA-3 (TRICOM). These TRICOM molecules engage with naïve T cells during antigen presentation to enhance the downstream activity of Th1, such as antigen-specific cytotoxic T-cell proliferation [14]. PROSTVAC is well tolerated [15, 16] and increases the avidity of cytotoxic T-cell against malignant cells [17]. A randomized phase II, placebo-controlled study enrolling 125 patients with mCRPC presented a median OS was 25.1 months for patients given PROSTVAC vs. 16.6 months for controls (HR=0.56; 95% CI: 0.37-0.85; *P*=0.0061) [18] and there was no difference in progression free survival (PFS) [18].

DCVAC/PCa

DCVAC/PCa is an autologous dendritic cell (DC) vaccine derived from peripheral blood mononuclear cells. The dendritic cells are obtained by apheresis, pulsed with killed prostate cancer cells, and then-after maturation-injected subcutaneously Podrazil et al. in 2015 published that DCVAC/PCa immunotherapy combined with chemotherapy in patients with mCRPC was well tolerated. Patients were also given 50 mg daily for 1 week oral cyclophosphamide to deplete regulatory T cells [19] and a topical Toll-like receptor agonist at the injection site to enhance immune activation. The authors presented that DCVAC/PCa immunotherapy with chemotherapy resulted in a median OS of 19 months. This compared favorably to both the Halabi nomogram-predicted OS of 11.8 months (HR=0.26; 95% CI: 0.13-0.51, P=0.0001) and the MSKCC nomogram-predicted OS of 13 months (HR=0.33; 95% CI: 0.17-0.63, P=0.0008) [20].

ProstAtak

ProstAtak transfers a herpes simplex virus thymidine kinase to tumor cells via an adenoviral vector. Combining ProstAtak with a prodrug creates cytotoxic and immunostimulatory effects [21] that are well tolerated [22]. Rojas-Martinez et al. in 2013 published that ProstAtak treatment had no significant adverse events related to the treatment and no late toxicities after median follow-up of 11.3 years [23]. In this

study, no patients developed metastases. After ProstAtak injection, serum PSA levels rose to a peak during week 1-2 and then fell prior to surgery in 8 of 9 patients. The authors concluded that ProstAtak was well tolerated and led to distribution throughout the intra-prostatic tumor with no significant toxicities.

Sipuleucel-T

Sipuleucel-T (Provenge) is an autologous cellular product derived from a patient's own harvested peripheral blood mononuclear cells. After harvest immature antigen-presenting cells (APCs) via leukapheresis, cells are incubated with a fusion protein (PA2024), which consists of prostatic acid phosphatase (PAP)-expressed in over 95% of PCa- and granulocyte-macrophage colony-stimulating factor GM-CSF) [24]. In the phase III IMPACT trial, among 512 patients with mCRPC, the median overall survival (OS) in patient receiving Sipuleucel-T was 25.8 months, compared to 21.7 months with placebo [25]. Neoadjuvant sipuleucel-T was associated with a 3-fold increase in activated T cells in 57% (95% CI: 39-79) of post-radical prostatectomy (RP) biopsies compared to pretreatment biopsies (P<0.001) [26-28].

Immune checkpoint inhibitors

T-cell activation is a complex process that requires stimulatory signal. T-cell receptor binding to MHC induces specificity to T-cell activation, but additional costimulatory signals are required. The CD28 receptor is constitutively expressed on the surface of T cells and undergoes activation by binding to B7 ligands (B7-1 and B7-2). CD28:B7-1/2 binding lead to proliferation of T cells, increased T-cell survival, and differentiation. Cytotoxic T-lymphocyte-associated protein-4 (CTLA-4) is a CD28 homolog with much higher binding affinity for B7 [29, 30]; however, binding of CTLA-4 to B7 does not induce a stimulatory signal [31, 32]. This competitive binding can inhibit the costimulatory signal normally provided by CD28:B7 binding [33-35]. The relative amount of CD28:B7 binding versus CTLA-4:B7 binding determines whether a T cell will undergo activation or deactivation [36]. Inhibition of CTLA-4 can shift the immune system balance toward T-cell activation with increased CD28:B7 binding, resulting in rejection of tumors by the host.

In a phase III trial of Kwon et al. in 2014, studying men with mCRPC refractory to docetaxel to receive bone-directed radiotherapy followed by ipilimumab (10 mg/kg) or placebo (n=799). The trial barely failed to meet its primary endpoint of demonstrating an improvement in median OS (11.2 months for ipilimumab versus 10.0 months for placebo; HR=0.85, P=0.053) [37]. However, statistically significant superior median PFS was seen (4.0 versus 3.0 months; HR=0.70; P<0.0001). In the other phase III study of Beer et al. in 2017, 400 chemotherapy-naïve patients with asymptomatic or minimally symptomatic mCRPC and no known visceral metastases were randomized 2:1 to receive up to 4 doses of ipilimumab 10 mg/kg or placebo every 3 weeks, followed by a maintenance dose every 3 months. There was no improvement in OS [38]. However, median PFS again favored ipilimumab (5.6 months versus 3.8 months; HR=0.67; 95% confidence interval (0.55-0.81)) [38]. PFS data and the subgroup analysis in the former study suggest a subset of patients with mCRPC may still benefit from ipilimumab therapy.

Programmed death 1 (PD-1) is a member of the B7/CD28 family of costimulatory receptors. It regulates T-cell activation through binding to its ligands, programmed death ligand 1 (PD-L1) and programmed death ligand 2 (PD-L2) [39]. PD-1 binding inhibits T-cell proliferation and reduces T-cell survival [39]. PD-1 functions primarily in peripheral tissues, where T cells may encounter the immunosuppressive PD-1 ligands PD-L1 (B7-H1) and PD-L2 (B7-DC), which are expressed by tumor cells, stromal cells, or both [40-43]. PD-1 is primarily expressed on activated T cells and pro-B cells; whereas, PD-L1 is expressed on T cells, APCs, vascular endothelial cells, stromal cells, and cancer cells [44, 45]. Inhibition of the interaction between PD-1 and PD-L1 can enhance T-cell responses in vitro and mediate preclinical antitumor activity [42, 46]. Small data sets from studies of PD-1/PD-L1 inhibition in prostate cancer have revealed modest activity [47] and confirmed PD-L1 expression in some [48, 49] but not all [50] tumor specimens. As single agents, immune checkpoint inhibitors have failed to substantially improve clinical outcomes in prostate cancer [47, 48, 50]. Increased expression of PD-L1 on circulating DCs has been observed in patients with enzalutamide-resistant prostate cancer, suggesting a role for

anti-PD-1/PD-L1 treatment in castration-resistant disease [48].

When tumor antigen specific T cells recognize their antigen, signaling through the T cell receptor (TCR) induces interferons (IFNs) [51] and simultaneously express activation-induced regulatory receptors including PD-1 [52]. The IFNs amplify the immune response and attracting other leukocytes such as natural killer (NK) cells and macrophages [53]. However, IFNs also increase the expression of IFN-inducible immune suppressive factors such as PD-L1 and indolamine 2, 3 dioxygenase [54, 55]. This is an adaptive process immune resistance that inhibits immune and inflammatory responses, and cancer uses this phenomenon to protect the tumor's growth. Frequently, cancer cells escape immune system and activate tumor growth using immunosuppressive mechanisms. Strongly or chronically activated T cells express more PD-1, and most cells express its ligand PD-L1 after exposure to T cell-derived IFNγ. In adaptive immune resistance process, these T cell response will increase suppression of activated CD8+ T cells [56].

While checkpoint inhibitor monotherapies have not substantially improved clinical outcomes for patients with prostate cancer, approaches that combine immune checkpoint inhibitors, vaccines, and other agents are under investigation to manipulate the immune system leading to increased antitumor activity.

Combinational immunotherapy

Even though there are many trials studying single agent immunotherapy, it has thus far demonstrated only modest survival benefit to mPCa. Consequently, new research efforts have focused on combination immunotherapy. For example, a completed phase I clinical trial was tested sipuleucel-T in combination with ipilimumab (NCT01832870) and an ongoing phase II trial testing this combination with sequence variation is recruiting subjects (NCT01804465). Two phase II studies were completed sipuleucel-T with enzalutamide in mCRPC (NCT01981122) and concurrent vs. sequential sipuleucel-T and abiraterone treatment in mCRPC (NCT01487863). A phase II study testing PROSTVAC with or without ipilimumab in the neoadjuvant setting is currently recruiting patients (NCT02506114). A phase I/II study currently underway combines a DNA vaccine encoding PAP plus pembrolizumab in sequence or concurrently in mCRPC patients (NCT02499835, NCT03248570, NCT02861573, and NCT02499835). A phase I/II study currently recruiting combines PROSTVAC with ipilimumab, nivolumab, or the triple combination (NCT02933255).

Pro-tumorigenic immune change by cancer and the effect of cytoreductive surgery

Thus far the literature examining changes to the immune system after cytoreductive prostate surgery remains sparse. As such we will review the effects of CRS among other cancers to provide insight into the effects of CRP.

Host immune response to various cancer has a strong influence on clinical outcomes [57, 58]. In particular, the presence of CD8+ tumor-infiltrating lymphocytes (TIL) is associated with prolonged PFS and overall survival [59-63]. Additionally, other features of cytolytic CD8+ T cell responses are also positively associated with survival [58]. CD8+ and CD20+ TIL showed the strongest association with survival [63]. In ovarian cancer, 73.1% (79/108) of tumors were positive for intraepithelial CD8+ TIL and 19.4% (20/103) contained intraepithelial CD20+ TIL [64]. Absolute lymphocyte count (ALC) and TIL are independent immunological parameters associated with outcome in high-grade serous carcinoma (HGSC). In the case of absolute lymphocyte count (ALC), this appears to reflect an association with disease burden rather than an immunological mechanism [64]. However, simply increasing ALC may not be sufficient to promote clinically significant antitumor responses. Several markers of inflammation have been associated with increased tumor burden and/or adverse outcome in ovarian cancer, including high neutrophil-to-lymphocyte ratio; high monocyte count [65]; elevated C-reactive protein and hypoalbuminaemia [66] and elevated IL-6 and IL-8 levels.

Helper T cells and cytotoxic T cells change by cancer

Type 1 T helper (Th1) and type 2 T helper (Th2) cells represent two polarized forms of the CD4+ Th cell-mediated specific immune responses. Th1-dominated immune responses predominantly produce a phagocyte-dependent inflam-

mation [67, 68]. Type 2 Th (Th2) cells secrete many cytokines such as IL4, IL5, IL6, IL9, IL10, and IL13, which inhibit several functions of phagocytic cells [69-72]. Decker et al. in 1996 and Ishikawa et al. in 2009 presented that changes in the ratio of Th1/Th2 CD4+ cells peak around 2-3 days following surgery, and return to normal levels by post-operative day 14 [73, 74]. Surgical stress induces a shift in the Th1/Th2 balance toward Th2, suggesting that cell-mediated immunity is down-regulated and antibody-mediated immunity is up-regulated after surgery.

T cells that secrete cytokines such as interferon gamma (IFN-γ) generate acute inflammation that results in expansion of cytotoxic T cells (CTLs). CTLs are a functional subset of the antigen specific immune response. The key immune cells for antitumor activity are the CTLs which directed against tumor cells susceptible to cell lysis [75]. The presence of antitumor CTLs is a prerequisite for the immune system to attack cancer cells. Immunomodulatory agents attempt to increase the efficacy of CTL activity. In 2003, Zhang et al. published that infiltration of CD3+, CD8+ cytotoxic T cells (CTL) is associated with a better prognosis for ovarian cancer patients [57, 59]. In colorectal cancer, it was reported that the T cell infiltration was good marker to predict disease free and OS more accurately compare with the standard TNM staging system [76, 77]. Tumor with highly infiltrated T cells and T cell with few T cells were identified retrospectively following CRS. The authors presented that a high T cells infiltrate in colorectal tumors predicts a good outcome of conventional therapy. In the head and neck squamous cell carcinoma (HNSCC), several investigators also published that high numbers of activated CD8+ effector T cells correlates with better survival [78-82]. On the other hand, a greater number of regulatory T cells (Tregs) in tumor infiltrating lymphocyte (TIL) have correlated with a poor prognosis [78-80].

Anti-tumorigenic effect of B-cells

B-cells mainly infiltrated lymphoid structures in the stroma of HGSC metastases. There was a strong B-cell memory response directed at a restricted repertoire of antigens. A positive role for B-cells in the antitumor response was also supported by B-cell depletion in a syngeneic mouse model of peritoneal metastasis. The authors showed that B-cells infiltrating HGSC omental metastases support the development of an antitumor response [83]. In preclinical models of melanoma, squamous cell carcinoma and carcinogen-induced skin cancer, B-cells promote tumor progression through the production of immune regulatory cytokines and immune complexes [84-86]. On the other hand, in human primary tumors, the presence of B-cells in association with tertiary lymphoid structures (TLS) in non-small cell lung carcinoma (NSCLC) and colorectal, ovarian, and pancreatic cancers has been associated with a better prognosis [87-89]. In primary ovarian cancer biopsies, intra-tumor infiltration of CD27-atypical memory B-cells, together with CD8+ T cells, is linked to better prognosis [90]. A very recent study also showed that a high infiltrate of B-cells in primary tumors is linked to the presence of TLS in the microenvironment and improved survival of patients [91]. Montfort et al. in 2017 studied that there was a strong B-cell memory response directed at a restricted repertoire of antigens and production of tumor-specific IgGs by plasma cells in 92 high-grade serous ovarian cancer (HGSOC). In that paper, B-cells were located mainly in lymphoid aggregates, which displayed characteristic features of TLS. There was no significant difference in the number of B-cells in pre and post NACT biopsies, suggesting that chemotherapy neither impairs nor increases B-cell infiltration in omental metastases. B-cells in HGSOC omentum are activated, differentiate to a memory B-cell phenotype and undergo clonal selection. B-cells are implicated in the recruitment of both DCs and granulocytes in omental metastases and more specifically in TLS. Human metastases of HGSOC, B-cells develop memory responses in the tumor microenvironment, likely via their association with TLS. In lung cancer, the presence of B-cell-rich TLS and DCs has been linked to good prognosis and the development of a Th1 signature [92]. Because activated DCs can stimulate CD8+ T cells and promote a cytotoxic response and B cells and DC densities were correlated in HGSOC metastases.

In early studies using murine models of B-cell deficiency, it was suggested that B-cells may actually inhibit the antitumor effect of tumor infiltrating T-cells [93, 94]. As a potential mechanism, B-cells have been demonstrated to inhibit the priming effect of CD4+ T-cells on

CD8+ T-cells [95]. Yang et al. presented that OS in patients undergoing primary and secondary debulking procedures was 160.6 months in those patients with low B-cell expression as compared to 47.3 months in those with high B-cell expression (P=0.0015) [96]. A greater extent of B-cell infiltration in omental tissue appears to correlate with poorer survival. Milne et al. suggests that tumor infiltrating B cells may be a positive prognostic marker [64].

M2 polarization of macrophages by cancer

Macrophages are classically categorized M1 or pro-inflammatory macrophages, included in the responses of type I helper T cells (Th1), or M2 or anti-inflammatory macrophages, involved in Th2-type responses [97]. M1 macrophages play key roles in the pro-inflammatory and anti-tumor responses and are induced by interferon (IFN) and lipopolysaccharide (LPS). M2 macrophages are activated by IL-4 and IL-13, and are responsible for angiogenesis and may assist tumor progression [98, 99]. Until now, the effect of tumor resection on immune system is very controversial. Zhu et al., in 2017 [100], measured tumor infiltrated with macrophages after surgery win glioblastoma patients. To determine whether macrophages were recruited to the tumor-debulking site, specimens were stained for CD68, which is general marker of tumor associated macrophages (TAM). Tumors from the debulking group exhibited a higher percentage of CD68+ cells (50% *vs.* 10%, debulking and non-debulking, respectively).

Prior studies have demonstrated that tumor-associated macrophage (TAM) infiltration promotes the progression of various malignancies [101-105]. Wan et al. in 2009 presented that the mean density of TAM was significantly higher in ovarian cancer than in benign ovarian lesions (57.7 vs. 25.3 per vision field, P<0.01). The 5-year survival rate was significantly higher in low-density TAM group than in high-density TAM group of ovarian cancer patients (73.3% vs. 41.2%, P=0.01) [106]. Similar results were published that macrophage infiltration is associated with poor prognosis in numerous malignant tumors [107, 108]. Lan et al. in 2013 published that expression of M2-polarized macrophages is associated with poor prognosis for advanced epithelial ovarian cancer [109]. No significant difference was observed in survival between patients in high- and the low-CD68 expression groups. In contrast, the PFS rates and OS rates were significantly higher in the low-CD163 expression group than in the high-CD163 expression group, respectively. Significantly improved 3-year PFS (49.8% vs. 11.0%, *P*<0.001) and OS (77.4% vs. 45.0%, *P*=0.001) rates in patients in the low-CD163/CD68 ratio group when compared with the high-CD163/CD68 ratio group was also observed. The authors concluded that infiltration of CD163-positive M2 macrophages as well as activation of macrophages towards the M2 phenotype may contribute to poor survival in advanced ovarian cancer. Cornelissen et al. in 2014 studied that ratio of intratumoral macrophage phenotype is a prognostic factor in epithelioid malignant pleural mesothelioma [110]. The number of CD68 and CD163 cells was comparable between the surgery and the non-surgery group, and was no changed in overall survival (OS) in groups. However, the CD163/CD68 ratio significantly correlated with OS in both in the total patient group. The total number of macrophages in tumor tissue did not correlate with OS in both groups, however, the CD163/CD68 ratio correlates with OS in the total patient group.

The primary tumor is believed to orchestrate and maintain the ideal microenvironment for tumor cell proliferation and subsequent metastases and the concept that immunologic intervention would alter the natural course offers unique insights into tumor progression and potential therapeutics.

Immuno-suppressive effect of dendritic cells

Plasmacytoid dendritic cells (pDC) and myeloid dendritic cells (mDC) are main subsets of human dendritic cells (DC) in blood. pDC are identified as a CD4+, CD11c, lineage marker, and HLADR+ cells that express CD123/IL-3 receptor alpha chain and/or as BDCA2- and BDCA4-expressing cells [111]. pDC link innate and adaptive immune responses by promoting the activation and differentiation of natural killer (NK) cells, B cells, myeloid DC (mDC), and T cells [112-114]. Tumor infiltration by pDC may have clinical importance, as underlined by their identification in tumors including melanoma, head and neck, lung, ovarian, and breast cancers [115, 116].

In ovarian cancer, several studies have shown an accumulation of pDC in malignant ascites fluid, with decreased blood concentration [115,

117, 118]. Ascites-originating pDC were shown to favor tumor angiogenesis via the production of TNFα and IL-8 [118]. Labidi-Galy et al. in 2011 presented that ascite pDC were 7.2-fold higher than patient blood pDC (P<0.001) and 13.8-fold higher than TApDC (P<0.001) [119]. mDC were present in malignant ascites but in lower proportions than pDC (P<0.001) while their presence in tumors was scarce. The authors presented that both TLRL-activated TApDC and ascite pDC were able to induce CD4+ T cell proliferation consistently with the acquisition of a fully mature phenotype. pDC play a proinflammatory role in malignant ascites, whereas they are immunosuppressive in tumors. IFN-a produced primarily from pDC, in addition to having direct anti-tumoral activity [120, 121], provides an important signal for T helper precursor differentiation in favor of a T helper type 1 immune response [122]. Zou and colleagues [115, 123] showing that pDC isolated from malignant ascites are functional in terms of IFN-a production. The authors detail that the accumulation of pDC in ascites (up to 10-fold higher than in tumors) had no impact on patients' outcome whereas their presence in tumors was deleterious. Moreover, the authors showed that TApDC were strongly inhibited for their innate response.

In other cancers such as breast and pancreatic cancer, blood pDC and mDC were significantly decreased compared with healthy control groups, consistent with prior studies [124, 125].

Cytokines for immune suppression

TGF-β and IL-10, were involved in tumor-induced immunosuppression [126-130]. Transforming growth factor beta (TGF-β) is a multifunctional cytokine, whose myriad of functions include its ability to potently suppress the immune system [131-134]. Interleukin 10 (IL-10) is a suppressive cytokine that is produced and released by immune cells such as macrophages, monocytes and different T-cell subsets, as well as by tumor cells. It down-regulates the macrophages function, inhibits the production of IL-2 and interferon γ (IFN-γ) by Th1-cells, as well as decreases the expression of MHC class I molecule on tumor cells, resulting in the development and promotion of cancer [135-138].

Maeda et al. in 1996 presented that sub-optimal primary surgery leads to unfavorable immunological changes in ovarian cancer patients. On the day of primary cytoreduction and 7 days after, the selected serum immunological parameters were determined in 49 patients with confirmed epithelial ovarian cancer (EOC) [130]. In that paper, the level of immunosuppressive (IL-10 and TGF-β1) and pro-inflammatory (IL-6 and IL-8) cytokines was significantly higher in the group of patients with advanced stage of disease, compared to early stage. The overall survival of patients who underwent optimal cytoreduction was significantly higher than that in whom only sub-optimal surgery was performed. Primary cytoreduction resulted in the decrease of both cytokines serum amount. However, in EOC patients with advanced stage of disease the TGF-β1 concentration, despite being lower, still remained intensified. It evidence that primary cytoreduction only partially reduced tumor-induced immunosuppression. Napoletano et al. (2010) [139] also claimed that solely IL-10 serum level decreased after surgery. Both optimal and suboptimal primary surgery weakened systemic immunosuppression in patients with stage III/IV through reduction of IL-10 and TGF-β1 serum level. However, it should be strongly underlined that the retained concentration of TGF-β1 in the serum of patients in whom only sub-optimal cytoreduction was performed was significantly higher in compare to its level in patients operated optimally. In contrast, we and others [140] noticed that there was no significant difference between the IL-10 level in relation to presence or absence of post-operative residual tumor. TGF-β or IL-10 can favor tumor growth and high immunosuppressive effects on T-cell mediated immunity [137, 141], as well as is considered to favor tumor growth and metastasis and its high concentration in tumor micro-environment correlates with poor patient outcome [142]. Li et al. in 2010 published that increase number of such regulatory T cells is associated with elevated concentration of TGF-β1 observed in patients in whom only sub-optimal operation was performed. TGFβ is known to convert $CD4^+CD25^-$ T cells to $CD4^+CD25^+$ T cells that maintains peripheral immune tolerance [143-146]. Moreover, Treg, observed in tumor microenvironment of EOC patients, therefore its high number in circulation could facilitate the creation of favorable environment for cancer cells [147]. Since partial removal of tumor mass did not reverse the

systemic immunosuppression we can assume that high serum level of TGF-β1 accompanied with enhanced number of $CD4^{+}CD25^{+high}$ cells in advanced EOC patients might contribute to the induction of T-cell suppression, thus allowing the metastases growth from postoperative residual tumor tissue. Similar results was published by Shashikant et al. in 2009 that sub-optimal cytoreduction resulted in unfavorable increase in the percentage of $CD4^{+}CD25^{+high}$ cells in peripheral blood as well as in insufficient decrease in serum concentration of TGF-β. However, the optimal cytoreduction could promote opportunity of ovarian cancer patients in III/IV stage of disease to improve PFS and OS [148].

Interleukin 6 (IL-6) signaling is generally considered pro-tumorigenic cytokine in various malignances [149-152]. However, Tempfer et al. in 1997 and Nowak et al. in 2010 presented that the serum concentration of IL-6 was markedly higher, mainly in EOC patients with advanced stage of the disease [153, 154] and primary cytoreduction both optimal and sub-optimal had no influence on its level.

The primary cytoreduction reduced the serum concentration of IL-8 of patients with FIGO stage III/IV, although sub-optimal surgical operation resulted in still high amount of it. Interleukin 8, is a pro-inflammatory cytokine and its overexpression in tumor microenvironment of ovarian cancer patients significantly correlates with disease severity and poor prognosis [155].

Conclusions

CRS has been explored in multiple tumor types [156-162]. Kidney cancer provides one of the most striking examples of the benefits CRS, as cytoreductive nephrectomy plus immunotherapy has previously demonstrated survival improvement [163-167]. However, as data and technical improvements in CRS as well as the role of immunotherapy continue to evolve, we may see expansion in CRS. In this paper, we overviewed about immunological change in the context of interaction of tumor and tumor microenvironment and the effect of CRS in immune system. The interaction between tumor and microenvironment such as immune cells derived to pro-tumorigenic such as M2 macrophages and Th2 cells and increased immunosuppressive cytokines such as TGF-β and IL-10. Therefore, we expected that CRS may decrease these driving forces and the combination with CRP and immunotherapy or chemotherapy may help to survival benefit. Still, there are little reports about immunological changed after CRP. If many ongoing clinical trial data analysis are accumulated, it can show the right way about CRP.

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Disclosure of conflict of interest

None.

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