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Reversal of Primary Resistance to Pembrolizumab With Intrapleural Hypotonic Cisplatin Treatment in a PD-L1 ≥ 50% Lung Adenocarcinoma Patient with Malignant Pleural Effusion

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Abstract

Currently standard first-line pembrolizumab monotherapy for highly selected non-small-cell lung cancer patients with PD-L1 expression ≥ 50% shows limited response in patients, with nearly half showing primary resistance. In addition, patients with malignant pleural effusion (MPE), which is suggested to be tumor-promoting and immunosuppressive, have worse responses. A 76-year-old man was diagnosed with left lower lobe lung adenocarcinoma cT2bN3M1a stage IVA with slight MPE. PD-L1 expression ≥ 50% was detected, along with no driver mutations. After three doses of pembrolizumab monotherapy, lung tumor growth with increased MPE was observed. Hypotonic cisplatin (15 mg cisplatin in 500 ml distilled water) was administered to the pleural cavity through a chest tube for pleurodesis. Five months later, tumor shrinkage and resolution of MPE after nine doses of pembrolizumab monotherapy were confirmed, with a robust response lasting over 20 months. As reported in in vitro and preclinical models, intrapleural hypotonic cisplatin was considered to trigger immune activation, possibly via immunogenic cell death, leading to reversal of resistance and a systemic immune response that was augmented by combination with pembrolizumab. Further clinical studies are needed to re-evaluate intrapleural hypotonic cisplatin therapy as a local immunotherapy in combination with systemic immunotherapy in patients with MPE.

Keywords: *Immunotherapy, resistance, immune checkpoint inhibitor, pembrolizumab, intrapleural hypotonic cisplatin, malignant pleural effusion, immunogenic cell death, local immunotherapy.*

1. Introduction

Immune checkpoint inhibitors (ICIs) that block the programmed cell death-1 (PD-1)/programmed cell death-ligand-1 (PD-L1) axis have dramatically improved the treatment outcomes of advanced non-small cell lung cancer (NSCLC) without driver mutations [1-5]. However, responses to ICIs only occur in a limited subset of patients, with many non-responders showing primary resistance. Acquired resistance is also common after a certain period, even in initial responders [6,7]. In initial phase 1 studies of nivolumab and pembrolizumab, PD-L1 expression on tumor cells observed via immunohistochemistry showed to enrich the populations with clinical benefit [8,9]. Subsequent clinical trials have shown the predictive ability of PD-L1 expression for NSCLC and melanoma outcomes [3,10]. PD-L1 is the most widely used predictive biomarker for ICI response in NSCLC. However, PD-L1 alone is not a perfect biomarker; approximately 10-20% of PD-L1 negative tumors achieve a response, while PD-L1 positive tumors do not always achieve a response [1-3,11-14]. First-line pembrolizumab monotherapy for NSCLC with a high PD-L1 tumor proportion score (PD-L1 TPS ≥ 50%) showed a higher objective response rate of 46.1% than platinum-based chemotherapy in the KEYNOTE-024 trial [12,13]. This shows that even in patients highly selected by the best available predictive biomarker, PD-L1 TPS, over half showed primary resistance to pembrolizumab monotherapy. Similar results were seen outside of clinical trials [14].

Besides PD-L1 immunostaining, alternative predictive or prognostic markers for ICI therapy for NSCLC have been reported from several retrospective studies, with varying levels of evidence. These markers include clinical characteristics, blood-based laboratory biomarkers, and genetic markers [15]. Clinical characteristic markers with preferable outcomes include male sex, Eastern Cooperative Oncology Group performance status (ECOG-PS) < 2, no use of steroids or antibiotics, body mass index (BMI) ≥ 25, and no metastasis to the liver or pleura. Blood-based laboratory biomarkers with preferable outcomes include low C-reactive protein (CRP) and lactate dehydrogenase (LDH) levels, and low baseline neutrophil-to-lymphocyte ratio (NLR; ≤ 5). As genetic markers, tumor mutation burden (TMB) on tissue and circulating tumor DNA (ctDNA), soluble PD-L1,

and oncogenic mutations, (i.e., mutations in Kirsten rat sarcoma viral oncogene homolog (KRAS), STK11, and TP53) have been investigated [16].

Malignant pleural effusion (MPE) is associated with worse progression-free survival (PFS), overall survival (OS), and response rates to ICI therapy [17-19]. In particular, MPE was significantly associated with a lack of response even in NSCLC with PD-L1 TPS ≥ 50% (OR 2.68; p=0.0228), as well as shorter progression-free survival (PFS; HR:1.52; p=0.043) after first-line pembrolizumab monotherapy in a multicenter observational study [20,21]. These studies suggest that pembrolizumab monotherapy is not a suitable first-line treatment for patients with MPE owing to the high likelihood of treatment failure, even in patients with a high PD-L1 TPS.

Some tumors may have additional immune escape mechanisms other than the PD-1/PD-L1 axis that cause primary resistance in non-responders to initial immunotherapy. Complex and varying immune escape mechanisms underlying ICI resistance have been elucidated, such as insufficient tumor antigenicity, alternate immune checkpoint overexpression, oncologic signaling pathways, and immunosuppressive tumor microenvironments, although the complete mechanisms are not fully understood [22,23]. Insufficient tumor antigenicity includes selection of subclones with loss of putative neoantigens and deficiencies in MHC class I antigen presentation due to loss of β2-microglobulin or interferon-γ (IFN-γ) signaling. Alternate immune checkpoint overexpression of T-cell immunoglobulin, mucin domain-3 protein (TIM-3), lymphocyte-activation gene 3 (LAG-3), B and T lymphocyte attenuator (BTLA), T-cell immunoreceptor tyrosine-based inhibition motif domain (TIGIT), and V-domain immunoglobulin-containing suppressor of T-cell activation (VISTA) leads to progressive T-cell exhaustion. Oncologic signaling pathways such as the mitogen-activated protein kinase (MAPK) pathway, loss of the tumor suppressor phosphatase and tensin homolog (PTEN), and WNT/β-catenin signaling, lead to altered immune cell composition (i.e., T-cell exclusion and decreased cytotoxic T-cell activity) in the tumor microenvironment. The tumor microenvironment contains immunosuppressive cells such as regulatory T cells (T-regs), myeloid-derived suppressor cells (MDSCs), and M2 tumor-associated macrophages (TAMs), along with increased production of inhibitory cytokines, such as transforming growth factor-β (TGF-β), interleukin-10 (IL-10), and vascular endothelial growth factor (VEGF). Considering the simultaneous occurrence of multiple immune escape mechanisms, targeting a single immune evasion mechanism with ICI monotherapy appears to be insufficient in non-responders. Thus, to increase the efficacy of ICI therapy in patients across various cancer types, combination therapies with ICIs are being investigated [24,25].

The tumor microenvironment of MPE has been recognized as both tumor-promoting and immunosuppressive [26-29]. In MPE, tumor cells, pleural mesothelial cells, and immune cells coexist and interact, leading to immune cell polarization to an immunosuppressive phenotype (M2 macrophages, N2 type neutrophils, T-regs) and abundant production of tumor-promoting (IL-6), immunosuppressive (TGF-β, IL-10, VEGF), and permeability-inducing mediators (VEGF, CCL2, angiopoietin) [30]. MPE-infiltrating T lymphocytes show a high CD4/CD8 ratio with decreased CD8+ effector-memory T cells, exhausted phenotype including increased levels of immune checkpoints (PD-1, TIM-3, and CTLA-4), and impaired cytotoxicity with reduced production of IFN-γ and granzyme B [31-33]. This is possibly due to M2-macrophage secreted TGF-β [33]. In addition, T-regs are increasingly recruited to MPE by macrophage-derived CCL22 [34-38]. However, the immunosuppressive tumor microenvironment of MPE may be reversed, as exemplified by IL-2 intrapleural administration [39]. In particular, the pleural space is a promising site for local intrapleural therapy with respect to accessibility via the chest tube, high local concentrations of therapeutic agents due to the sequestered pleural space, and direct contact between drugs, tumors, and immune cells. Many intrapleural immunotherapies and chemotherapies for MPE have shown promise in clinical trials [27,28]. The combination of ICI and intrapleural therapy warrants further investigation to improve the responses to ICI in lung cancer patients with MPE.

To date, few studies have reported the successful reversal of ICI primary resistance in lung cancer, especially in patients with MPE. We report the first case in which intrapleural hypotonic cisplatin treatment reversed primary resistance to pembrolizumab monotherapy and restored activity in a PD-L1 ≥ 50% NSCLC patient with MPE.

2. Case presentation

A 76-year-old man with a smoking history of 110-pack-years was diagnosed with left lower lobe lung adenocarcinoma cT2bN3M1a, stage IVA, with a slight volume of MPE (Figure 1A).

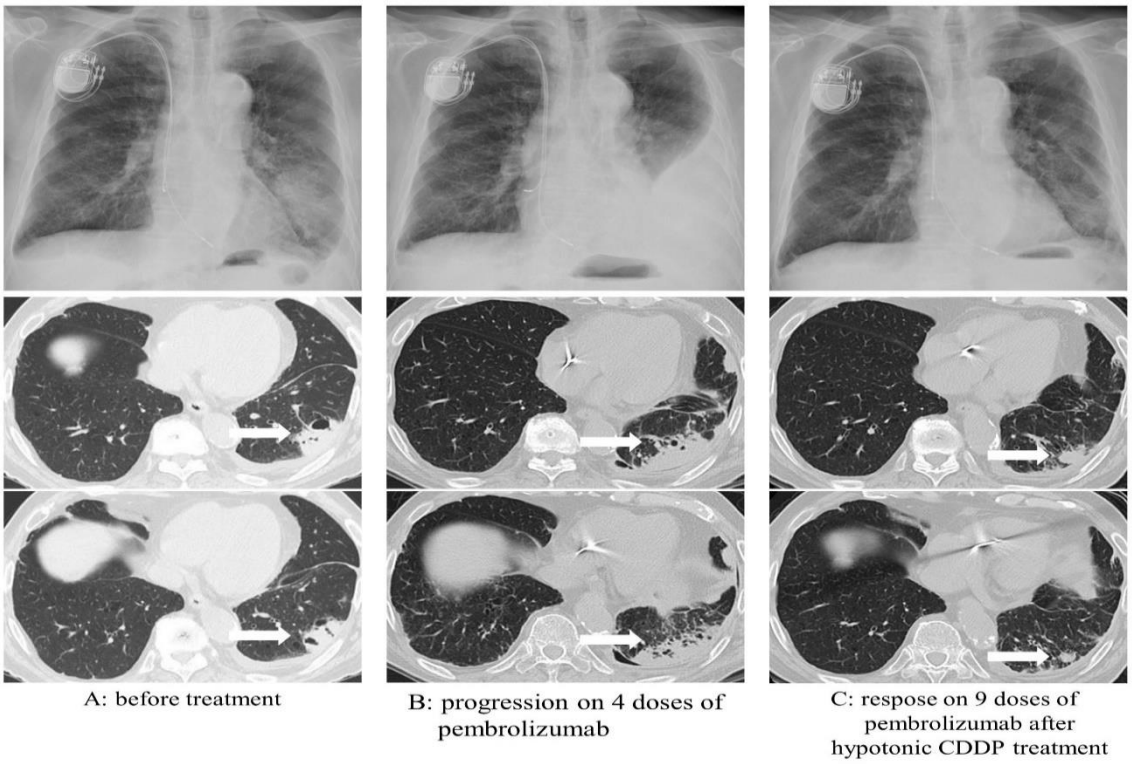

Figure 1: (A) The patient was diagnosed with cT2bN3M1a, Stage IVA lung adenocarcinoma, with ipsilateral slight malignant pleural effusion (MPE). (B) During treatment, MPE progressed. After 4 doses of pembrolizumab, enlargement of the primary lung tumor was confirmed. Pleural drainage and intrapleural hypotonic cisplatin were administered. (C) After hypotonic cisplatin treatment, the MPE disappeared, and partial response was confirmed after 9 doses of pembrolizumab monotherapy.

He was medicated for hypertension and had no history of treatments requiring admission. Neither driver mutations in EGFR nor translocations of ALK and ROS1 were detected. PD-L1 immunohistochemistry yielded a TPS ≥ 50%. Owing to the simultaneous diagnosis of complete atrioventricular blockage and symptomatic cardiac failure, he was initially given a permanent pacemaker implantation. Two weeks later, as he recovered to ECOG PS 1, he was administered an initial dose of 200 mg pembrolizumab monotherapy as the first-line lung adenocarcinoma treatment. A grade 1 pruritic rash was observed on the back and lower extremities in the first week. Small amounts of diuretics (20 mg furosemide and 25 mg spironolactone) were prescribed to prevent pleural fluid accumulation due to cardiac failure. Pembrolizumab was continued for the third doses in the outpatient clinic. The amount of left MPE increased gradually, and the patient complained of appetite loss and cough. Two months after the initial pembrolizumab dose, the patient was readmitted for MPE control. He lost 1.2 kg from 62.8 kg at the time of initial pembrolizumab administration to 61.6 kg on readmission. His blood examination was unremarkable, with normal liver and renal functions, electrolytes, white blood cells, NLR of 3.5, LDH (160 IU/L), a slight decrease in albumin (2.8 g/dl) and hemoglobin (9.3 g/dl), and elevated CRP (6.45mg/dl). Pleural drainage with a chest tube was performed, and bloody discharge was observed. After complete drainage of the MPE, negative pressure suction (-10 to -20 cmH2O) was applied to expand the trapped lung. The fourth dose of pembrolizumab was administered during pleural drainage, as scheduled. The cytology of pleural effusion revealed a huge amount of adenocarcinoma cells. Chest computed tomography (CT) during chest tube drainage revealed enlargement of the primary lung tumor, along with cavitated pleural free space with a thickened visceral pleural membrane, suggestive of a trapped lung (Figure 1B). As for tumor marker on diagnosis and after two months on readmission, CEA slightly declined from 10.7 ng/ml to 6.6 ng/ml (normal range < 5.0 ng/ml); however, SLX increased from 54 U/ml to 76 U/ml (normal range < 38.0 U/ml). Thus, based on clinical information, imaging, and tumor marker deterioration, the tumor was evaluated as a progressive disease, showing primary resistance to pembrolizumab. To treat pleurodesis and promote lung expansion by resolving the thickened visceral carcinomatous pleural membrane, hypotonic cisplatin (CDDP; 15 mg CDDP dissolved in 500 ml distilled water with 10 mL of 1% lidocaine) was administered into the pleural cavity through a chest tube. The infused agents were drained after an hour. No adverse effects were observed during or after the procedure. The MPE was controlled, and the chest tube was removed 9 days after hypotonic CDDP administration, with a total drainage period of 26 days. His appetite had recovered well by the time of discharge. The patient continued pembrolizumab treatment in the outpatient clinic. Five months after discharge, a partial response to pembrolizumab monotherapy after nine doses was confirmed on chest CT with lung tumor shrinkage and resolution of the MPE (Figure 1C). At this time, he had gained 5.6 kg of body weight (from 61.6 kg to 67.2 kg). The patient survived 20 months after diagnosis in good condition (ECOG PS 1), with maintenance of tumor response up to 23 doses of pembrolizumab at the time of reporting. Adverse effects of pembrolizumab including grade 2 arthritis, grade 2 diarrhea, and grade 2 rash were observed in the course of treatment, and low-dose prednisolone (no more than 5 mg daily) was prescribed for 6 months.

3. Discussion

This case demonstrated primary resistance to pembrolizumab in lung adenocarcinoma with TPS ≥ 50% and MPE. Primary resistance was overcome with pleural drainage and a singular administration of intrapleural hypotonic CDDP along with continuation of pembrolizumab, and a robust response was observed, lasting more than 20 months. While the exact mechanisms underlying resistance reversal were not investigated in this patient, intrapleural hypotonic CDDP is believed to trigger an activating immune reaction, eliminate suppressive mechanisms in the pleural cavity, or both. The following sections describe several important mechanisms that reverse resistance to pembrolizumab.

First, intrapleural hypotonic CDDP can induce reversal of resistance to pembrolizumab via immunogenic cell death (ICD) of tumor cells. Demontoux et al. demonstrated this mechanism in vitro and in a preclinical model of peritoneal carcinomatosis [40]. Their results showed that temporary exposure to hypotonic CDDP and hypotonic oxaliplatin could decrease cancer cell viability than isotonic conditions. Moreover, hypotonic treatment induced ICD to activate immune responses to carcinoma cells, which was not achieved with isotonic conditions. In an in vivo murine peritoneal carcinomatous model, hypotonic oxaliplatin strongly improved mouse survival compared to isotonic oxaliplatin via an immune-dependent mechanism of increased CD8+ T cell infiltration and activation, which validates the efficacy of hypoosmotic treatments. Although hypotonic CDDP was not investigated in an in vivo model, similar efficacy is expected, considering the comparable ability of hypotonic CDDP in inducing ICD.

The ICD of tumor cells is a functionally peculiar type of regulated cell death which can be recognized by immune cells to elicit adaptive antitumor immune responses, with immunological memory against dead cell-derived tumor-associated antigens (TAAs). Vaccination of immunocompetent syngeneic mice with cancer cells killed by ICD inducers in vitro can help develop adaptive anticancer immunity and immunological memory against TAAs. Thus, ICD is protective against developing tumors after subcutaneous rechallenge with live cancer cells via an immune response [41,42]. ICD requires spatiotemporally coordinated emission of immunostimulatory damage-associated molecular patterns (DAMPs) from dying cells, such as cell surface exposure of calreticulin (CALR), extracellular adenosine triphosphate (ATP), and extracellular high mobility group box 1 (HMGB1) release. Induction of ICD leads to the recruitment of dendritic cells (DCs) into the tumor, phagocytosis of dying cells by DCs, DC maturation, antigen presentation to T cells, and production of IL-1β to elicit tumor-specific IFN-γ-producing cytotoxic T cells (CTLs) [41-43].

Considering the ability of hypotonic CDDP to induce ICD, its combination with ICIs could have a synergistic effect in cancer immunotherapy. Some in vivo cancer model studies have demonstrated that chemotherapy-induced ICD can sensitize tumors to anti-PD-1/PD-L1 checkpoint inhibitors [44-49]. In these studies, chemotherapy using agents with ICD-inducing capacities had better efficacy than chemotherapy without ICD in controlling tumor growth. As a mechanism to sensitize cells to anti-PD-1/PD-L1 checkpoint inhibitors, chemotherapy-induced ICD resulted in increased tumor infiltration and higher functionality of CD8+ T cells (granzyme B, IFN-γ, tumor necrosis factor α (TNF-α)), even in tumors that initially lack T cell infiltration [44-49]. Additionally, CD8+ T cell activation depended on increased frequency of the DC-macrophage-like subset (CD11b+ CD11c+ Ly-6G-Ly-6C-) with upregulated toll-like receptor 4 (TLR4), which is the receptor of HMGB1 and required DCs for antigen presentation [46]. Anticancer immunity induced by ICD in the pleural cavity combined with pembrolizumab might affect both the local pleural cavity directly and distant lung primary lesions via a systemic response.

In contrast to the ICD-inducing capacity of anthracyclines (doxorubicin, idarubicin, epirubicin) and oxaliplatin, CDDP is generally considered a non-ICD inducer due to its weak ability to trigger the endoplasmic reticulum (ER) stress response, which leads to pre-apoptotic CALR exposure to the plasma membrane surface [50,51]. However, CDDP can occasionally induce CALR exposure depending on cell type, drug concentration, and exposure time [48,52]. Moreover, CDDP-induced ICD can be achieved by combination therapy with agents that trigger CALR exposure, such as digoxin, digitoxin, crizotinib, and ER stressing agents thapsigargin, tunicamycin, pyridoxine, and zinc dichloride [45,51,53-57]. In particular, hypotonic conditions have been shown to enhance the ability of CDDP to induce ICD [40]. As indicated in the study, this may be associated with increased platinum incorporation into cancer cells via oligomerization of copper transporter 1 (CTR1), the membrane copper transporter related to platinum uptake. Increased cellular platinum uptake by reduced osmolarity has been reported to result in greater cytotoxicity [58,59]. Thus, although in ordinary conditions, intravenous CDDP is unable to induce ICD by itself, it can be said that cisplatin can induce ICD independently in some specific conditions, or with the help of other agents. Hypotonic CDDP can be applied through the intracavitary route to induce ICD, but not intravenously. Other administration route, such as direct intratumor injection might be investigated to take advantage of ICD inducing ability in the future. Considering that only one administration of hypotonic CDDP led to reversal of resistance to pembrolizumab and durable response, ICD-induced TAA recognition and establishment of immunological memory may be compatible explanations for our findings.

Second, some additional immunomodulatory effects of CDDP, other than ICD, may contribute to resistance reversal. The anticancer activity of CDDP is derived not only from direct cytotoxicity via cross-linking of DNA and interference of transcription and DNA replication, but also from anticancer immunomodulation, as reviewed by de Biasi et al. and Hato et al. [60,61] De Biasi et al. [60] described that CDDP can affect the immune system through four main mechanisms: upregulation of MHC class I expression, promotion of immune cell recruitment and proliferation, enhancement of the lytic ability of cytotoxic cells (through perforin/granzyme or Fas/FasL mechanisms), and downregulation of immunosuppressive tumor microenvironments [62]. Insufficient tumor antigenicity, such as losses of putative neoantigens or deficiencies in MHC class I antigen presentation, have been proposed as possible mechanisms of resistance to PD-1/PD-L1 blockade. MHC class I upregulation by CDDP chemotherapy may be synergistic with pembrolizumab by restoring antigen presentation and CD8+ T cell recognition [63-65]. Additional non-synonymous mutations caused by CDDP exposure can also

enhance antigenicity [65]. PD-L1 upregulation induced by CDDP has also been demonstrated to synergize with PD-L1 blockade [65-69]. In addition, CDDP has been reported to inhibit immunosuppressive cells such as T-regs and MDSCs [70,71]. These mechanisms could provide additional explanations for CDDP's ability to reinstate pembrolizumab efficacy. However, it is hard to solely explain the resistance reversal of the primary lung lesion in our case by these mechanisms, as it was not directly treated with CDDP.

Third, pleural fluid drainage, which eliminates immunosuppressive cells and mediators in MPE, might explain the increased response to pembrolizumab. MPE represents a tumor-promoting, immunosuppressive, and functionally 'cold' microenvironment despite its abundance of immune cells and mediators [27]. Innate immune cells, such as mast cells, macrophages, neutrophils, DCs, and natural killer (NK) cells, together with pleural mesothelial cells and tumor cells, exist as immunosuppressive phenotypes such as M2 polarized TAMs, N2 type neutrophils, immunosuppressive DCs, and poorly cytotoxic, proangiogenic NK cells. This occurs through the production of platelet-derived growth factor (PDGF), IL-8, VEGF, nitric oxide, monocyte chemotactic protein 1 (MCP-1), leukotriene B4, epithelial neutrophil-activating peptide-78 (ENA-78), chemokine ligand 18 (CCL18), IL-1β, tryptase alpha/beta-1 (TSAB1), CCL 12, osteopontin, TNF-α, and TGF-β [27,30]. Adaptive immune cells create an immunosuppressive microenvironment in MPE [27]. T-regs are recruited to MPEs via CXCL1, CXCR2, and CCL22 chemokine signaling. In contrast, recruitment of natural killer T (NKT) cells and B cells is decreased in MPEs. B cell function is inhibited by increased soluble CD40 in MPEs due to competition for CD 154 on T cells. MPE-infiltrating T cells show a high CD4/CD8 ratio with increased central memory CD4+ T cells and decreased CD8+ effector T cells [31,32]. Effector CD8+ T cell downregulation is associated with increased expression of immune checkpoints (PD-1, TIM-3, and LAG-3) and impaired T cell cytotoxicity with reduced production of IFN-γ and granzyme B [33]. Some mechanisms of decreased CD8+ effector T cells have been proposed, such as incomplete differentiation into effector cells due to negative regulation by the PD-1/PD-L1 axis and activation-induced cell death (AICD) due to upregulated expression of Fas ligand (FasL) and tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) [72,73]. Removal of these localized immunosuppressive cells and mediators might induce an immune-susceptible state that promotes response of primary lung lesions to systemic pembrolizumab.

Intrapleural hypotonic CDDP can be regarded as a local immunotherapy, especially when an immunomodulatory effect is expected. In our case, it was successfully combined with systemic pembrolizumab immunotherapy. The pleural cavity is a suitable site for local drug delivery because of its accessibility and closed containment. Locally administered drugs can achieve direct contact with tumor surface areas and sufficient local concentrations with relatively low doses, reducing the possibility of systemic adverse effects [28]. Local immunotherapy is gaining attention and is being evaluated in combination with systemic immunotherapy [74,75]. Considering its potent ability to induce ICD, local intrapleural hypotonic CDDP therapy can be expected to generate robust antitumor immune responses against broader and more immunogenic neoantigens in the pleural cavity. Moreover, systemic responses of distant lesions can be anticipated, especially when combined with systemic immunotherapy, via activated tumor antigen-specific lymphocytes moving into the systemic circulation or lymphatics. Whether the response of the primary lung lesion is an adjacent or distant response cannot be distinguished in our case. However, if the response of the primary lung lesion is a product of systemic immunity to distant lesions, this therapy is expected to be effective for distant metastatic lesions.

The efficacy and safety of intrapleural hypotonic cisplatin treatment were evaluated in a phase II trial that included 80 patients [76]. Intramuscular pentazocine (15 mg) and intrapleural (10 ml) 1% lidocaine were administered as premedication. Thereafter, 25 mg CDDP in 500 ml distilled water was administered through a chest tube, and the tube was clamped for 1 h. The patients were requested to roll around their body to disperse the drug during treatment. The overall response rate of effusion and median effusion PFS were 83% (complete plus partial responses) and 173 days, respectively, with no hematological toxicity. Non-hematological toxicities of grade 3 (nausea, vomiting, pyothorax, and dyspnea) were observed in less than 5% of patients. This efficacy is acceptable when compared to other commonly used sclerosing agents such as talc, tetracycline, and OK432. It should be mentioned that the mechanism and efficacy of hypotonic cisplatin treatment completely differ from those of widely reported isotonic cisplatin agents dissolved in saline. As reviewed by Shiozaki et al. [77], hypotonic stress of distilled water itself can induce significant cytocidal effects on cancer cells, that is, cell swelling and then cell rupture following short-time exposure (within 3-10 min). In addition, the increased uptake of cisplatin by tumor cells treated with hypotonic cisplatin dissolved in distilled water leads to greater cell lysis than isotonic cisplatin treatment [58,59]. Furthermore, the ability to induce ICD, eliciting adaptive antitumor immune responses, is demonstrated recently as described above, which is not achieved with isotonic cisplatin [40]. Our patient was treated with a similar procedure using a reduced dose of 15 mg CDDP. Revaluating intrapleural hypotonic CDDP therapy as a localized immunotherapy in combination with systemic PD-1/PD-L1 inhibitors in patients with MPE is of value, as this method can be easily implemented clinically.

Among various mediators in MPE, VEGF has been recognized as a critical factor for the fluid accumulation of MPE by increasing vascular permeability and promoting angiogenesis [78]. Many studies have reported favorable control of MPE by intrapleural or intravenous bevacizumab, a VEGF inhibitor, combined with or without chemotherapy, although treatment protocols, regimens, and efficacy assessment definitions are heterogeneous [79-84]. In intrapleural bevacizumab studies, effusion response rate and median effusion PFS are reported at approximately 78–86% and 115–159 days [79-82]. In two phase II intravenous bevacizumab studies in Japan, pleural effusion control rate at eight weeks and pleural PFS without re-accumulation of MPE were reported at approximately 81–93% and 13.9–16.6 months, respectively [83-84]. Improved management of MPE by intrapleural bevacizumab compared to intrapleural cisplatin (isotonic) has also been demonstrated in a study [82]. It is widely accepted that bevacizumab is indispensable in treating MPE. However, although the accurate comparison is difficult due to different study designs,

intrapleural hypotonic cisplatin treatment showed a comparable response rate (83%) and even better median effusion PFS (173 days) compared to intrapleural bevacizumab therapy, as described above [76]. Regarding the studies on the intravenous bevacizumab, several cycles of bevacizumab plus chemotherapy and additional maintenance of bevacizumab until disease progression were administered, which can be implemented only in fit patient populations. Certain cases are unsuitable for intravenous bevacizumab, such as those characterized by older age, risk of hemorrhage, poor PS, and later line of therapy. Nonetheless, intrapleural hypotonic CDDP therapy can be a therapeutic option due to its comparable efficacy, which may be implemented even in unfit patients.

VEGF contributes to immunosuppression in the tumor microenvironment through several mechanisms, inhibiting CTL trafficking, proliferation, and effector function, inhibiting DC maturation and antigen presentation, recruitment and proliferation of immunosuppressive cells (T-regs, MDSCs, and M2 TAMs), and angiogenesis leading to hypoxia and acidosis (low pH), in turn resulting in immunosuppression [85,86]. This scenario resembles the immunosuppressive tumor microenvironment of MPE. Vascular normalization by anti-angiogenesis like bevacizumab is considered to convert the immunosuppressive tumor microenvironment to an immunosupportive one. In phase III randomized controlled clinical trial IMpower150 study, bevacizumab has shown additive efficacy in NSCLC when combined with carboplatin, paclitaxel, and a PD-L1 inhibitor, atezolizumab [87]. However, the efficacy in patients with MPE or the ICD mediated synergism of bevacizumab-containing immunochemotherapy have not been reported, yet [88]. Considering combination treatment with ICIs, intrapleural hypotonic cisplatin which has potential ICD inducing capacity may outperform bevacizumab beyond controlling MPE, yielding systemic effects, as shown in our patient.

4. Conclusion

In conclusion, this case illustrates reversal of primary resistance to pembrolizumab via pleural drainage and a single administration of intrapleural hypotonic CDDP in a patient with lung adenocarcinoma with a PD-L1 TPS ≥ 50% and MPE. Intrapleural hypotonic CDDP is hypothesized to trigger activating immune reactions, possibly via an ICD mechanism that was augmented by combination with pembrolizumab, leading to a systemic immune response. To the best of our knowledge, this is the first single case report to describe the potential ICD-mediated response to intrapleural hypotonic CDDP in a patient. Further clinical studies to evaluate intrapleural hypotonic CDDP therapy as a local immunotherapy in combination with systemic PD-1 inhibitors in patients with MPE are valuable as this regimen has the potential to benefit many patients who show resistance to immunotherapy due to MPE.

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Consent for publication

Written informed consent was obtained from the patient for the publication of this case report and any accompanying images.

Conflicts of Interest

The authors report there are no competing interests to declare.

Author contributions: Koken Ameku drafted the original manuscript. All authors contributed to data acquisition and critical review. All authors have read and approved the final version of the manuscript to be published.

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References

1. Borghaei H, Paz-Ares L, Horn L, Spigel DR, Steins M, et al. Nivolumab versus Docetaxel in Advanced Nonsquamous Non-Small-Cell Lung Cancer. N Engl J Med. 2015;373(17):1627-1639. doi: 10.1056/NEJMoa1507643.
2. Brahmer J, Reckamp KL, Baas P, Crinò L, Eberhardt WE, et al. Nivolumab versus Docetaxel in Advanced Squamous-Cell Non-Small-Cell Lung Cancer. N Engl J Med. 2015;373(2):123-135. doi: 10.1056/NEJMoa1504627.
3. Herbst RS, Baas P, Kim DW, Felip E, Pérez-Gracia JL, et al. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. Lancet. 2016;387(10027):1540-1550. doi: 10.1016/S0140-6736(15)01281-7.
4. Rittmeyer A, Barlesi F, Waterkamp D, Park H, Ciardiello F, et al. Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): a phase 3, open-label, multicentre randomised controlled trial. Lancet. 2017;389(10066):255-265. doi: 10.1016/S0140-6736(16)32517-X.
5. Reck M, Remon J, Hellmann MD. First-Line Immunotherapy for Non-Small-Cell Lung Cancer. J Clin Oncol. 2022;40(6):586-597. doi: 10.1200/JCO.21.01497.
6. Sharma P, Hu-Lieskovan S, Wargo JA, Ribas A. Primary, Adaptive, and Acquired Resistance to Cancer Immunotherapy Cell. 2017;168(4):707-723. doi: 10.1016/j.cell.2017.01.017.
7. Gettinger SN, Wurtz A, Goldberg SB, Rimm D, Schalper K, et al. Clinical Features and Management of Acquired Resistance to PD-1 Axis Inhibitors in 26 Patients With Advanced Non-Small Cell Lung Cancer. J Thorac Oncol. 2018;13(6):831-839. doi: 10.1016/j.jtho.2018.03.008.
8. Topalian SL, Hodi FS, Brahmer JR, Gettinger SN, Smith DC, et al. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. N Engl J Med. 2012;366(26):2443-2454. doi: 10.1056/NEJMoa1200690.
9. Garon EB, Rizvi NA, Hui R, Leighl N, Balmanoukian AS, et al. Pembrolizumab for the treatment of non-small-cell lung cancer. N Engl J Med. 2015;372(21):2018-2028. doi: 10.1056/NEJMoa1501824.
10. Gibney GT, Weiner LM, Atkins MB. Predictive biomarkers for checkpoint inhibitor-based immunotherapy. Lancet Oncol. 2016;17(12):e542-e551. doi: 10.1016/S1470-2045(16)30406-5.
11. Chae YK, Oh MS, Giles FJ. Molecular Biomarkers of Primary and Acquired Resistance to T-Cell-Mediated Immunotherapy in Cancer: Landscape, Clinical Implications, and Future Directions. Oncologist. 2018;23(4):410-421. doi: 10.1634/theoncologist.2017-0354.

12. Reck M, Rodríguez-Abreu D, Robinson AG, Hui R, Csőszi T, et al. Pembrolizumab versus Chemotherapy for PD-L1-Positive Non-Small-Cell Lung Cancer. N Engl J Med. 2016;375(19):1823-1833. doi: 10.1056/NEJMoa1606774.
13. Reck M, Rodríguez-Abreu D, Robinson AG, Hui R, Csőszi T, et al. Five-Year Outcomes with Pembrolizumab Versus Chemotherapy for Metastatic Non-Small-Cell Lung Cancer With PD-L1 Tumor Proportion Score ≥ 50. J Clin Oncol. 2021;39(21):2339-2349. doi: 10.1200/JCO.21.00174.
14. Amrane K, Geier M, Corre R, Léna H, Léveiller G, et al. First-line pembrolizumab for non-small cell lung cancer patients with PD-L1 ≥50% in a multicenter real-life cohort: The PEMBREIZH study. Cancer Med. 2020;9(7):2309-2316. doi: 10.1002/cam4.2806.
15. Brueckl WM, Ficker JH, Zeitler G. Clinically relevant prognostic and predictive markers for immune-checkpoint-inhibitor (ICI) therapy in non-small cell lung cancer (NSCLC). BMC Cancer. 2020;20(1):1185. doi: 10.1186/s12885-020-07690-8.
16. Havel JJ, Chowell D, Chan TA. The evolving landscape of biomarkers for checkpoint inhibitor immunotherapy. Nat Rev Cancer. 2019;19(3):133-150. doi: 10.1038/s41568-019-0116-x.
17. Kang DH, Chung C, Kim JO, Jung SS, Park HS, et al. Pleural or pericardial metastasis: A significant factor affecting efficacy and adverse events in lung cancer patients treated with PD-1/PD-L1 inhibitors. Thorac Cancer. 2018;9(11):1500-1508. doi: 10.1111/1759-7714.12877.
18. Shibaki R, Murakami S, Shinno Y, Matsumoto Y, Goto Y, et al. Malignant pleural effusion as a predictor of the efficacy of anti-PD-1 antibody in patients with non-small cell lung cancer. Thorac Cancer. 2019;10(4):815-822. doi: 10.1111/1759-7714.13004.
19. Adachi Y, Tamiya A, Taniguchi Y, Enomoto T, Azuma K, et al. Predictive factors for progression-free survival in non-small cell lung cancer patients receiving nivolumab based on performance status. Cancer Med. 2020;9(4):1383-1391. doi: 10.1002/cam4.2807.
20. Morita M, Tamiya M, Fujimoto D, Tamiya A, Suzuki H, et al. Prediction of patients with a tumor proportion score > 50% who do not respond to first-line monotherapy with pembrolizumab. BMC Cancer. 2020;20(1):93. doi: 10.1186/s12885-020-6582-4.
21. Kawachi H, Tamiya M, Tamiya A, Ishii S, Hirano K, et al. Association between metastatic sites and first-line pembrolizumab treatment outcome for advanced non-small cell lung cancer with high PD-L1 expression: a retrospective multicenter cohort study. Invest New Drugs. 2020;38(1):211-218. doi: 10.1007/s10637-019-00882-5.
22. Ajina R, Zahavi DJ, Zhang YW, Weiner LM. Overcoming malignant cell-based mechanisms of resistance to immune checkpoint blockade antibodies. Semin Cancer Biol. 2020; 65:28-37. doi: 10.1016/j.semcancer.2019.12.005.
23. Fares CM, Van Allen EM, Drake CG, Allison JP, Hu-Lieskovan S. Mechanisms of Resistance to Immune Checkpoint Blockade: Why Does Checkpoint Inhibitor Immunotherapy Not Work for All Patients? Am Soc Clin Oncol Educ Book. 2019; 39:147-164. doi: 10.1200/EDBK_240837.
24. Attili I, Passaro A, Pavan A, Conte P, De Marinis F, et al. Combination immunotherapy strategies in advanced non-small cell lung cancer (NSCLC): Does biological rationale meet clinical needs? Crit Rev Oncol Hematol. 2017; 119:30-39. doi: 10.1016/j.critrevonc.2017.09.007.
25. Leonetti A, Wever B, Mazzaschi G, Assaraf YG, Rolfo C, et al. Molecular basis and rationale for combining immune checkpoint inhibitors with chemotherapy in non-small cell lung cancer. Drug Resist Updat. 2019; 46:100644. doi: 10.1016/j.drup.2019.100644.
26. Prado-Garcia H, Romero-Garcia S, Aguilar-Cazares D, Meneses-Flores M, Lopez-Gonzalez JS. Tumor-induced CD8+ T-cell dysfunction in lung cancer patients..Clin Dev Immunol. 2012; 2012:741741. doi: 10.1155/2012/741741.
27. Murthy P, Ekeke CN, Russell KL, Butler SC, Wang Y, et al. Making cold malignant pleural effusions hot: driving novel immunotherapies. Oncoimmunology. 2019;8(4):e1554969. doi: 10.1080/2162402X.2018.1554969.
28. Murthy V, Katzman D, Sterman DH. Intrapleural immunotherapy: An update on emerging treatment strategies for pleural malignancy. Clin Respir J. 2019;13(5):272-279. doi: 10.1111/crj.13010.
29. Donnenberg AD, Luketich JD, Dhupar R, Donnenberg VS. Treatment of malignant pleural effusions: the case for localized immunotherapy. J Immunother Cancer. 2019;7(1):110. doi: 10.1186/s40425-019-0590-4.
30. Stathopoulos GT, Kalomenidis I. Malignant pleural effusion: tumor-host interactions unleashed. Am J Respir Crit Care Med. 2012;186(6):487-492. doi: 10.1164/rccm.201203-0465PP.
31. Prado-Garcia H, Aguilar-Cazares D, Flores-Vergara H, Mandoki JJ, Lopez-Gonzalez JS. Effector, memory and naïve CD8+ T cells in peripheral blood and pleural effusion from lung adenocarcinoma patients. Lung Cancer. 2005;47(3):361-371. doi: 10.1016/j.lungcan.2004.07.046.
32. Scherpereel A, Grigoriu BD, Noppen M, Gey T, Chahine B, et al. Defect in recruiting effector memory CD8+ T-cells in malignant pleural effusions compared to normal pleural fluid. BMC Cancer. 2013; 13:324. doi: 10.1186/1471-2407-13-324.
33. Li L, Yang L, Wang L, Wang F, Zhang Z, et al. Impaired T cell function in malignant pleural effusion is caused by TGF-β derived predominantly from macrophages. Int J Cancer. 2016;139(10):2261-2269. doi: 10.1002/ijc.30289.
34. Wang D, Yang L, Yue D, Cao L, Li L, et al. Macrophage-derived CCL22 promotes an immunosuppressive tumor microenvironment via IL-8 in malignant pleural effusion. Cancer Lett. 2019; 452:244-253. doi: 10.1016/j.canlet.2019.03.040.
35. DeLong P, Carroll RG, Henry AC, Tanaka T, Ahmad S, et al. Regulatory T cells and cytokines in malignant pleural effusions secondary to mesothelioma and carcinoma. Cancer Biol Ther. 2005;4(3):342-346. doi: 10.4161/cbt.4.3.1644.
36. Chen YQ, Shi HZ, Qin XJ, Mo WN, Liang XD, et al. CD4+CD25+ regulatory T lymphocytes in malignant pleural effusion. Am J Respir Crit Care Med. 2005;172(11):1434-1439. doi: 10.1164/rccm.200504-588OC.
37. Qin XJ, Shi HZ, Deng JM, Liang QL, Jiang J, et al. CCL22 recruits CD4-positive CD25-positive regulatory T cells into malignant pleural effusion. Clin Cancer Res. 2009;15(7):2231-2237. doi: 10.1158/1078-0432.CCR-08-2641.

38. Budna J, Kaczmarek M, Kolecka-Bednarczyk A, Spychalski Ł, Zawierucha P, et al. Enhanced Suppressive Activity of Regulatory T Cells in the Microenvironment of Malignant Pleural Effusions. J Immunol Res. 2018;2018:9876014. doi: 10.1155/2018/9876014.
39. Hu CY, Zhang YH, Wang T, Chen L, Gong ZH, et al. Interleukin-2 reverses CD8(+) T cell exhaustion in clinical malignant pleural effusion of lung cancer. Clin Exp Immunol. 2016;186(1):106-114. doi: 10.1111/cei.12845.
40. Demontoux L, Derangère V, Pilot T, Thinselin C, Chevriaux A, et al. Hypotonic stress enhances colon cancer cell death induced by platinum derivatives and immunologically improves antitumor efficacy of intraperitoneal chemotherapy. Int J Cancer. 2019;145(11):3101-3111. doi: 10.1002/ijc.32590.
41. Kroemer G, Galluzzi L, Kepp O, Zitvogel L. Immunogenic cell death in cancer therapy. Annu Rev Immunol. 2013; 31:51-72. doi: 10.1146/annurev-immunol-032712-100008.
42. Kepp O, Senovilla L, Vitale I, Vacchelli E, Adjemian S, et al. Consensus guidelines for the detection of immunogenic cell death. Oncoimmunology. 2014;3(9): e955691. doi: 10.4161/21624011.2014.955691.
43. Di Blasio S, Wortel IM, van Bladel DA, de Vries LE, Duiveman-de Boer T, et al. Human CD1c(+) DCs are critical cellular mediators of immune responses induced by immunogenic cell death. Oncoimmunology. 2016;5(8):e1192739. doi: 10.1080/2162402X.2016.1192739.
44. D'Amico L, Menzel U, Prummer M, Müller P, Buchi M, et al. A novel anti-HER2 anthracycline-based antibody-drug conjugate induces adaptive anti-tumor immunity and potentiates PD-1 blockade in breast cancer. J Immunother Cancer. 2019;7(1):16. doi: 10.1186/s40425-018-0464-1.
45. Liu P, Zhao L, Pol J, Levesque S, Petrazzuolo A, et al. Crizotinib-induced immunogenic cell death in non-small cell lung cancer. Nat Commun. 2019;10(1):1486. doi: 10.1038/s41467-019-09415-3.
46. Pfirschke C, Engblom C, Rickelt S, Cortez-Retamozo V, Garris C, et al. Immunogenic Chemotherapy Sensitizes Tumors to Checkpoint Blockade Therapy. Immunity. 2016;44(2):343-354. doi: 10.1016/j.immuni.2015.11.024.
47. Yamazaki T, Buqué A, Ames TD, Galluzzi L. PT-112 induces immunogenic cell death and synergizes with immune checkpoint blockers in mouse tumor models. Oncoimmunology. 2020;9(1):1721810. doi: 10.1080/2162402X.2020.1721810.
48. Sakakibara K, Sato T, Kufe DW, VonHoff DD, Kawabe T. CBP501 induces immunogenic tumor cell death and CD8 T cell infiltration into tumors in combination with platinum, and increases the efficacy of immune checkpoint inhibitors against tumors in mice. Oncotarget. 2017;8(45):78277-78288. doi: 10.18632/oncotarget.20968.
49. Keep O, Zitvogel L, Kroemer G. Clinical evidence that immunogenic cell death sensitizes to PD-1/PD-L1 blockade. Oncoimmunology. 2019;8(10):e1637188. doi: 10.1080/2162402X.2019.1637188.
50. Tesniere A, Schlemmer F, Boige V, Kepp O, Martins I, et al. Immunogenic death of colon cancer cells treated with oxaliplatin. Oncogene. 2010;29(4):482-491. doi: 10.1038/onc.2009.356.
51. Martins I, Keep O, Schlemmer F, Adjemian S, Tailler M, et al. Restoration of the immunogenicity of cisplatin-induced cancer cell death by endoplasmic reticulum stress. Oncogene. 2011;30(10):1147-1158. doi: 10.1038/onc.2010.500.
52. Rébé C, Demontoux L, Pilot T, Ghiringhelli F. Platinum Derivatives Effects on Anticancer Immune Response. Biomolecules. 2019;10(1):13. doi: 10.3390/biom10010013.
53. Bezu L, Gomes-de-Silva LC, Dewitte H, Breckpot K, Fucikova J, et al. Combinatorial strategies for the induction of immunogenic cell death. Front Immunol. 2015;6:187. doi: 10.3389/fimmu.2015.00187.
54. Menger L, Vacchelli E, Adjemian S, Martins I, Ma Y, et al. Cardiac glycosides exert anticancer effects by inducing immunogenic cell death. Sci Transl Med. 2012;4(143):143ra99. doi: 10.1126/scitranslmed.3003807.
55. Škubník J, Pavlíčková V, Rimpelová S. Cardiac Glycosides as Immune System Modulators. Biomolecules. 2021;11(5):659. doi: 10.3390/biom11050659.
56. Aranda F, Bloy N, Pesquet J, Petit B, Chaba K, et al. Immune-dependent antineoplastic effects of cisplatin plus pyridoxine in non-small-cell lung cancer. Oncogene. 2015;34(23):3053-3062. doi: 10.1038/onc.2014.234.
57. Cirone M, Garufi A, Di Renzo L, Granato M, Faggioni A, et al. Zinc supplementation is required for the cytotoxic and immunogenic effects of chemotherapy in chemoresistant p53-functionally deficient cells. Oncoimmunology. 2013;2(9):e26198. doi: 10.4161/onci.26198.
58. Smith E, Brock AP. The effect of reduced osmolarity on platinum drug toxicity. Br J Cancer. 1989;59(6):873-875. doi: 10.1038/bjc.1989.185.
59. Kondo A, Maeta M, Oka A, Tsujitani S, Ikeguchi M, et al. Hypotonic intraperitoneal cisplatin chemotherapy for peritoneal carcinomatosis in mice. Br J Cancer. 1996;73(10):1166-1170. doi: 10.1038/bjc.1996.225.
60. de Biasi AR, Villena-Vargas J, Adusumilli PS. Cisplatin-induced antitumor immunomodulation: a review of preclinical and clinical evidence. Clin Cancer Res. 2014;20(21):5384-5391. doi: 10.1158/1078-0432.CCR-14-1298.
61. Hato SV, Khong A, de Vries IJM, Lesterhuis WJ. Molecular pathways: the immunogenic effects of platinum-based chemotherapeutics. Clin Cancer Res. 2014;20(11):2831-2837. doi: 10.1158/1078-0432.CCR-13-3141.
62. Ramakrishnan R, Assudani D, Nagaraj S, Hunter T, Cho HI, et al. Chemotherapy enhances tumor cell susceptibility to CTL-mediated killing during cancer immunotherapy in mice. J Clin Invest. 2010;120(4):1111-1124. doi: 10.1172/JCI40269.
63. Tran L, Allen CT, Xiao R, Moore E, Davis R, et al. Cisplatin Alters Antitumor Immunity and Synergizes with PD-1/PD-L1 Inhibition in Head and Neck Squamous Cell Carcinoma. Cancer Immunol Res. 2017;5(12):1141-1151. doi: 10.1158/2326-6066.CIR-17-0235.
64. Park SJ, Ye W, Xiao R, Silvin C, Padget M, et al. Cisplatin and oxaliplatin induce similar immunogenic changes in preclinical models of head and neck cancer. Oral Oncol. 2019; 95:127-135. doi: 10.1016/j.oraloncology.2019.06.016.
65. Grabosch S, Bulatovic M, Zeng F, Ma T, Zhang L, et al. Cisplatin-induced immune modulation in ovarian cancer mouse models with distinct inflammation profiles. Oncogene. 2019;38(13):2380-2393. doi: 10.1038/s41388-018-0581-9.

66. Fournel L, Wu Z, Stadler N, Damotte D, Lococo F, et al. Cisplatin increases PD-L1 expression and optimizes immune check-point blockade in non-small cell lung cancer. Cancer Lett. 2019; 464:5-14. doi: 10.1016/j.canlet.2019.08.005.
67. Ock CY, Kim S, Keam B, Kim S, Ahn YO, et al. Changes in programmed death-ligand 1 expression during cisplatin treatment in patients with head and neck squamous cell carcinoma. Oncotarget. 2017;8(58):97920-97927. doi: 10.18632/oncotarget.18542.
68. Tsai TF, Lin JF, Lin YC, Chou KY, Chen HE, et al. Cisplatin contributes to programmed death-ligand 1 expression in bladder cancer through ERK1/2-AP-1 signaling pathway. Biosci Rep. 2019;39(9): BSR20190362. doi: 10.1042/BSR20190362.
69. Shin J, Chung JH, Kim SH, Lee KS, Suh KJ, et al. Effect of Platinum-Based Chemotherapy on PD-L1 Expression on Tumor Cells in Non-small Cell Lung Cancer. Cancer Res Treat. 2019;51(3):1086-1097. doi: 10.4143/crt.2018.537.
70. Huang X, Chen YT, Song HZ, Huang GC, Chen LB. Cisplatin pretreatment enhances anti-tumor activity of cytokine-induced killer cells. World J Gastroenterol. 2011;17(25):3002-3011. doi: 10.3748/wjg.v17.i25.3002.
71. Van Wigcheren GF, De Haas N, Mulder TA, Horrevorts SK, Bloemendal M, et al. Cisplatin inhibits frequency and suppressive activity of monocytic myeloid-derived suppressor cells in cancer patients. Oncoimmunology. 2021;10(1):1935557. doi: 10.1080/2162402X.2021.1935557. eCollection 2021.
72. Prado-Garcia H, Romero-Garcia S, Puerto-Aquino A, Rumbo-Nava U. The PD-L1/PD-1 pathway promotes dysfunction, but not "exhaustion", in tumor-responding T cells from pleural effusions in lung cancer patients. Cancer Immunol Immunother. 2017;66(6):765-776. doi: 10.1007/s00262-017-1979-x.
73. Prado-Garcia H, Romero-Garcia S, Morales-Fuentes J, Aguilar-Cazares D, Lopez-Gonzalez JS. Activation-induced cell death of memory CD8+ T cells from pleural effusion of lung cancer patients is mediated by the type II Fas-induced apoptotic pathway. Cancer Immunol Immunother. 2012;61(7):1065-1080. doi: 10.1007/s00262-011-1165-5.
74. Bilusic M, Gulley JL. Local Immunotherapy: A Way to Convert Tumors From "Cold" to "Hot". J Natl Cancer Inst. 2017;109(12):djx132. doi: 10.1093/jnci/djx132.
75. Donnenberg VS, Wagner PL, Luketich JD, Bartlett DL, Donnenberg AD. Localized Intra-Cavitary Therapy to Drive Systemic Anti-Tumor Immunity. Front Immunol. 2022;13: 846235. doi: 10.3389/fimmu.2022.846235. eCollection 2022.
76. Seto T, Ushijima S, Yamamoto H, Ito K, Araki J et al. Intrapleural hypotonic cisplatin treatment for malignant pleural effusion in 80 patients with non-small-cell lung cancer: a multi-institutional phase II trial. Br J Cancer. 2006;95(6):717-721. doi: 10.1038/sj.bjc.6603319.
77. Shiozaki A, Ichikawa D, Kosuga T, Marunaka Y, Otsuji E. Regulation of osmolality for cancer treatment. J Physiol Sci. 2017;67(3):353-360. doi: 10.1007/s12576-017-0528-x.
78. Bradshaw M, Mansfield A, Peikert T. The role of vascular endothelial growth factor in the pathogenesis, diagnosis and treatment of malignant pleural effusion. Curr Oncol Rep. 2013(3):207-216. doi: 10.1007/s11 912-013-0315-7.
79. Nie K, Zhang Z, You Y, Zhuang X, Zhang C, et al. A randomized clinical study to compare intrapleural infusion with intravenous infusion of bevacizumab in the management of malignant pleural effusion in patients with non-small-cell lung cancer. Thorac Cancer. 2020(1):8-14. doi: 10.1111/1759-7714.13238.
80. Song X, Chen D, Guo J, Kong L, Wang H, et al. Better efficacy of intrapleural infusion of bevacizumab with pemetrexed for malignant pleural effusion mediated from nonsquamous non-small cell lung cancer. Onco Targets Ther. 2018; 11:8421-8426. doi: 10.2147/OTT.S184030. eCollection 2018.
81. Chen D, Song X, Shi F, Zhu H, Wang H, et al. Greater efficacy of intracavitary infusion of bevacizumab compared to traditional local treatments for patients with malignant cavity serous effusion. Oncotarget. 2017;8(21):35262-35271. doi: 10.18632/oncotarget.13064.
82. Du N, Li X, Li F, Zhao H, Fan Z, et al. Intrapleural combination therapy with bevacizumab and cisplatin for non-small cell lung cancer-mediated malignant pleural effusion. Oncol Rep. 2013;29(6):2332-2340. doi: 10.3892/or.2013.2349.
83. Usui K, Sugawara S, Nishitsuji M, Fujita Y, Inoue A, et al. A phase II study of bevacizumab with carboplatin-pemetrexed in non-squamous non-small cell lung carcinoma patients with malignant pleural effusions: North East Japan Study Group Trial NEJ013A. Lung Cancer. 2016; 99:131-136. doi: 10.1016/j.lungcan.2016.07.003.
84. Noro R, Kobayashi K, Usuki J, Yomota M, Nishitsuji M, et al. Bevacizumab plus chemotherapy in nonsquamous non-small cell lung cancer patients with malignant pleural effusion uncontrolled by tube drainage or pleurodesis: A phase II study North East Japan Study group trial NEJ013B. Thorac Cancer. 2020;11(7):1876-1884. doi: 10.1111/1759-7714.13472.
85. Fukumura D, Kloepper J, Amoozgar Z, Duda DG, Jain RK. Enhancing cancer immunotherapy using antiangiogenics: opportunities and challenges. Nat Rev Clin Oncol. 2018;15(5):325-340. doi: 10.1038/nrclinonc.2018.29.
86. Ren S, Xiong X, You H, Shen J, Zhou P. The Combination of Immune Checkpoint Blockade and Angiogenesis Inhibitors in the Treatment of Advanced Non-Small Cell Lung Cancer. Front Immunol. 2021 Jun 2;12: 689132. doi: 10.3389/fimmu.2021.689132. eCollection 2021.
87. Socinski MA, Jotte RM, Cappuzzo F, Orlandi F, Stroyakovskiy D, et al. Atezolizumab for First-Line Treatment of Metastatic Nonsquamous NSCLC. N Engl J Med. 2018;378(24):2288-2301. doi: 10.1056/NEJMoa1716948.
88. Reck M, Mok TSK, Nishio M, Jotte RM, Cappuzzo F, et al. Atezolizumab plus bevacizumab and chemotherapy in non-small-cell lung cancer (IMpower150): key subgroup analyses of patients with EGFR mutations or baseline liver metastases in a randomised, open-label phase 3 trial. Lancet Respir Med. 2019;7(5):387-401. doi: 10.1016/S2213-2600(19)30084-0.