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A case of Inoperable Chemotherapy-resistant Pleural Mesothelioma Treated with Subcutaneous Administration of Inactivated Sendai Virus Particles (HVJ-E) and Concurrent Chemotherapy for the First Time after the HVJ-E P-I Trial

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Abstract

We have previously conducted a P-I clinical trial using inactivated Sendai virus particles (HVJ-E: Hemagglutinating virus of Japan envelope), which have anti-tumor immune activation and direct anti-tumor activity in patients with inoperable chemotherapy-resistant malignant pleural mesothelioma (MPM). We report on the first experience of a patient enrolled in this clinical trial who was treated with continuous subcutaneous administration of HVJ-E with another chemotherapy regimen at the same time. After PD evaluation in the preceding P-I clinical trial, the patient started chemotherapy with gemcitabine and CPT-11 and received subcutaneous HVJ-E. HVJ-E has been used in the past as a single reagent for pleural mesothelioma, melanoma, and prostate cancer in the past as clinical studies and P-I clinical trials. This was the first time that HVJ-E was administered in combination with chemotherapy, and no serious adverse events were observed that could be caused by HVJ-E or chemotherapy were observed in that time. We have reported a valuable case that will be useful in combining HVJ-E with other treatments in the future, as we report the details of this case.

Keywords: Malignant Pleural Mesothelioma (MPM), Hemagglutinating Virus of Japan Envelope (HVJ-E), Concurrent Chemotherapy

1. Introduction

Malignant pleural mesothelioma (MPM) is an intractable pleural tumor caused by environmental factors, often occurring after asbestos exposure [1], and its prognosis is poor compared with other tumors [2]. Historically, chemotherapy (cisplatin and pemetrexed) has been the mainstay of treatment for MPM [2], with occasional extra pleural pleurectomy or pleural decortication for only limited cases (lesion) [3], because radical surgical resection is difficult to perform due to its intrapleural spread and invasion of the heart and other intrapleural organs [4], and radiotherapy sometimes used as adjuvant therapy [5]. In these situations, the outcome of the treatment for MPM was not satisfactory for a long time [6]. With the adaptation of immune checkpoint inhibitors (ICIs) to MPM, combination treatments with ICIs themselves, or chemotherapy are now being performed and as the first line treatment for sarcomatoid and other histological types of MPM [7], however the outcomes are still not as satisfactory as those for lung cancer [8]. Since the advent of ICIs, new treatments also have been developed, particularly focusing on anti-tumor immunotherapy [9]. We are developing a new treatment using HVJ-E, which has anti-tumor immune activation and direct anti-tumor effects. Previous *in vivo* results showed a high add-on effect in combination therapy of HVJ-E and chemotherapy [10]. Therefore, we administered HVJ-E and other chemotherapy concurrently for the first time to the chemotherapy-resistant MPM patient who had been enrolled in the P-I clinical trial that was using HVJ-E as a single reagent before ICIs was covered by insurance in Japan. This concurrent administration was a valuable experience for the future use of HVJ-E in combination with other therapies such as chemotherapy and ICIs, so we report it in detail.

2. Material and Methods

2.1 Preparation of HVJ-E

HVJ-E was manufactured by Ishihara Sangyo Kaisha, Ltd. (Osaka, Japan). Details of the manufacturing process of HVJ-E have been described in a previous paper [11].

2.2 Clinical research overview

For patients who participated in the preceding investigator-initiated clinical trial "Dose-escalation, tolerability, and efficacy of intratumoral and subcutaneous injection of hemagglutinating virus of Japan envelope (HVJ-E) for chemotherapy-resistant malignant pleural mesothelioma: A clinical trial (P-I)," at the time of enrollment, there were no treatments with proven efficacy other than standard chemotherapy (cisplatin and pemetrexed) (no second-line treatments). In cases where HVJ-E administration in the preceding investigator-initiated clinical trial did not result in clear PD in tests of tumor lesions, etc., and the patient requested continued administration after completion of P-I, that is, only in cases what a response suggesting efficacy was observed in the clinical trial, continued subcutaneous administration of HVJ-E (subcutaneous administration only, no intratumoral administration) was to be performed.

The inclusion criteria were based on the P-I clinical trial, and patients were enrolled if they met the inclusion and exclusion criteria, did not have PD at the evaluation immediately after the P-I clinical trial, and wished to continue receiving HVJ-E [12].

In addition, the protocol treatment was discontinued in any of the following events to ensure the safety and ethics of the subjects and getting adequate evaluation:

1. The patient may withdraw consent
2. If the patient's circumstances make it impossible to continue the clinical trial in accordance with this clinical trial
3. If continuation of the clinical trial is difficult due to worsening of the underlying disease after the start of treatment
4. Grade 4 hematologic or non-hematologic toxicity based on Common Terminology Criteria for Adverse Events (CTCAE ver. 4.0) related to the administration of the test drug is observed
5. If an adverse event is observed and the clinical trial principal investigator (subinvestigator) judges that it is difficult to continue the clinical trial for that subject
6. If the clinical trial principal investigator (subinvestigator) judges that it is appropriate to discontinue the clinical trial for other reasons.

In this clinical trial, the possibility of continued administration was considered every three cycles of protocol treatment, and the protocol treatment was completed when it was determined that continued administration will not be performed. Treatment after progression or recurrence after completion of protocol treatment was not specified. Furthermore, treatment was not specified after discontinuation of protocol treatment.

This continuous study after the P-I clinical trial (#157908) was conducted as a physician-initiated clinical trial after passing our university IRB (#16291-2).

2.3 Treatment schedule

The study design was a non-randomized, open-label, single-center study.

The HVJ-E was administered subcutaneously four times over two weeks, followed by a two-week rest period (which might be extended to four weeks due to concomitant medication schedules), for a total of four to six weeks of treatment per cycle, which would be repeated three times.

The administered HVJ-E dose was the same as that in the Phase I clinical trial. In other words, in the P-I high-dose group, each vaccination was 60,000 mNAU, and the total amount in one cycle was 240,000 mNAU.

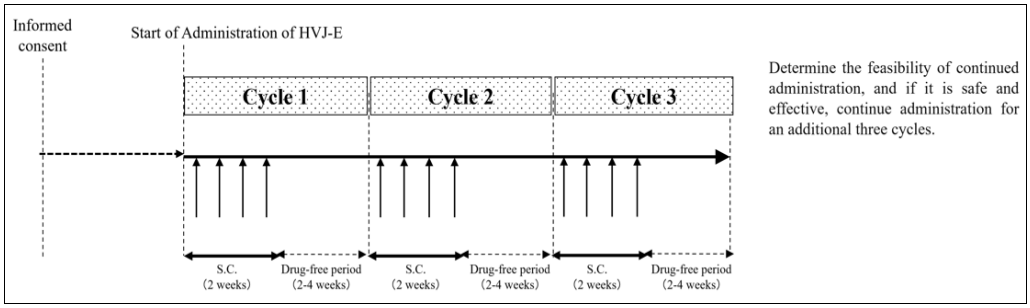

Fig 1: Clinical trial timeline of the study protocol

After completion of the preceding P-I, patients were screened within 3 weeks prior to study's entry and received a subcutaneous injection of HVJ-E into the chest wall near the tumor on day 1. A total of 3 subcutaneous injections of HVJ-E were administered within 2 weeks. A total of 12 injections of HVJ-E were going to be administered over 3 cycles. HVJ-E: Inactivated hemagglutinating virus of Japan envelope; MPM, malignant pleural mesothelioma.

2.4 Criteria for resuming HVJ-E administration if postponed

In an adverse event that makes it difficult to continue administration in this clinical trial, the next administration may be postponed for up to one week, and the case will still be evaluated even if administration is postponed.

In addition, administration may be resumed if the investigator determines that the adverse event that caused administration to be delayed has resolved or improved, and dosing can be resumed.

2.5 Concomitant use of drugs

After informed consent has been obtained, the following medications and therapies are prohibited because they may interfere with the safety of the subjects and the evaluation of this study.

1. immunosuppressants (cyclophosphamide, etc.)
2. Corticosteroids (prednisolone, dexamethasone, etc.)
3. Other investigational drugs
4. Radiotherapy.

2.6 Safety assessment

Safety and adverse events were evaluated according to the Common Terminology Criteria for Adverse Events (CTCAE) ver. 4.0.

3. Results and Discussion

3.1 Case

The patient was a 66-year-old man who had chest and back pain for 20XX-3 months and was diagnosed with pleural mesothelioma (epitheloid, T3 non-penetrating pericardial invasion, N0M0 stage IB (UICC ver. 8)) at a nearby hospital in 20XX. One month later, 1st line chemotherapy with cisplatin and pemetrexed was started and 6 courses were administered. The patient was evaluated as partial response but progressed to progressive disease (PD). Seven months later, the patient entered a clinical trial of 2nd line; defactinib (FAK inhibitor); however, the patient was judged to have PD after 4 months and the trial was discontinued. Three months later, the 3rd line; cisplatin and pemetrexed) was tried again, but was judged to have PD after 6 months. Fourth line; tremelimumab (anti-CTLA-4 Ag.) was started but was discontinued after 2 months because of the development of toxic rash. Although SD was maintained, the patient was deemed to have PD 7 months after discontinuation. Nine months after discontinuation of tremelimumab, the patient participated in the 5th line; HVJ-E P-I clinical trial and successfully completed the 2-month HVJ-E P-I clinical trial period as a high-does group. The patient's disease was maintained SD during the clinical trial, but it was judged to occur 1.25 months after the end of the clinical trial. Two months after the end of the clinical trial (20XX+37 months), the 6th line chemotherapy, CPT-11, and gemcitabine, was started. The second chemotherapy of the first course was postponed on the 7th day after the start of chemotherapy due to myelosuppression, low sodium, and suspicious febrile neutropenia, and chemotherapy was administered on the 14th day after the start of chemotherapy. The second course of chemotherapy was also postponed due to neutropenia, and the 2nd course of chemotherapy was administered 7 months after the end of the clinical trial. Then, the 3rd course was postponed again due to neutropenia. Eventually, 4.5 months after the end of the clinical trial, the first chemotherapy of the 3rd course was administered on June 20, and then the first subcutaneous administration of HVJ-E was administered 2 days after the chemotherapy. Four days later, the second administration of HVJ-E was done, three days later the third administration, and four days later the fourth administration were done. During this time, chemotherapy was postponed due to myelosuppression, and the second chemotherapy of the 3rd course was done the day after the 1st cycle of HVJ-E. The fourth course of chemotherapy was scheduled approximately 4 weeks after the latest chemotherapy, but because palpitations due to pericardial effusion were observed, chemotherapy and HVJ-E treatment were discontinued and treatment such as pericardial drainage was performed. The continuation of the clinical trial is difficult due to worsening of the underlying disease after the start of treatment, and the second and subsequent cycles of HVJ-E were discontinued. One month after the drainage of pericardial effusion, two courses of 7th-line vinorelbine (VNR) were administered, and pericardial fenestration was performed two months later due to pericardial effusion. One more course of VNR was done; however, it was ineffective, and the patient was deceased approximately two months later. It was 10 months after the end of clinical trial.

A: Trend in neutrophil counts.

B: The trend in platelet counts. Areas of adverse event grades according to CTCAE ver.4.0 are shown as yellow and red bands.

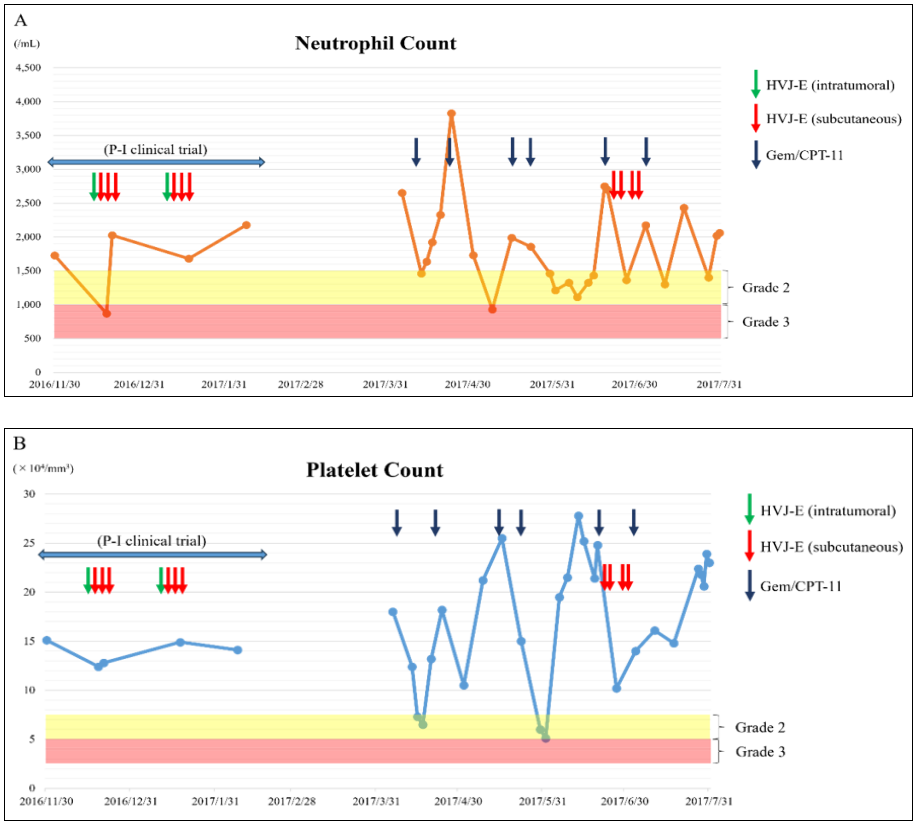

Fig 2: Trends in the laboratory data

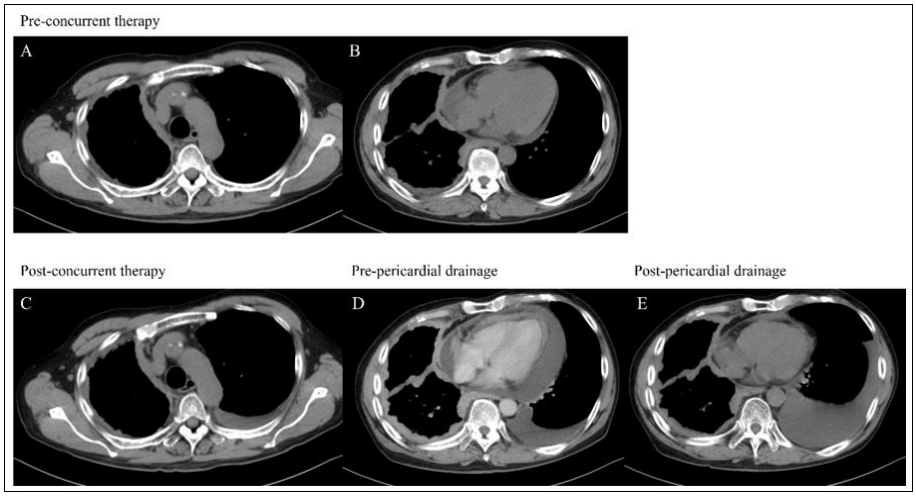

Fig 3: CT images

A, B: CT image of the chest at pre-concurrent therapy. C: CT image of the chest at the post-concurrent therapy. D: CT image of the heart immediately before pericardial drainage. E: CT image of the heart immediately after pericardial drainage with increased pleural effusion.

3.2 Discussion

It has been reported that certain chemotherapeutic reagents activate anti-tumor immunity [13], and such mechanisms have been reported for CPT-11 and gemcitabine used in this study [14-21].

We have conducted clinical trials using HVJ-E as a single reagent in melanoma, prostate cancer, and MPM, and in basic research we have reported that combining HVJ-E with cisplatin or immune checkpoint inhibitors such as a PD-1 antibody in MPM-bearing mouse models may have a synergistic effect [12]. Therefore, combination therapy with HVJ-E and chemotherapeutic reagents is expected to be more useful than either reagent alone in clinical trials, but combination therapy with HVJ-E has not been performed in clinical trials. Therefore, we performed combination therapy with late-line chemotherapy and HVJ-E for the first time in a patient after P-I with HVJ-E alone.

In clinical trials of HVJ-E in advanced melanoma and castration-resistant prostate cancer, adverse events for which a causal relationship with HVJ-E could not be excluded included fever, fatigue, injection site reactions (erythema, pruritus), leukopenia, lymphopenia, and neutropenia. However, all such events were brief and well tolerated [22-25].

In the Phase I study of HVJ-E in MPM, the most common adverse events associated with HVJ-E were systemic symptoms such as fever (83.3%), local symptoms such as skin induration (83.3%), and local injection-related events such as injection site reactions (100%), all of which were transient [12].

In the P-I of this case, Grade 2 or higher adverse events for which a causal relationship could not be denied included neutropenia (G-3), injection site reactions (G-2), and leukopenia (G-2), but these were also transient.

In the treatment of MPM, CPT-11, gemcitabine, and vinorelbine are still occasionally employed as late-line treatments [26], but frequent adverse events have been observed to include leukopenia, neutropenia and thrombocytopenia [27-29].

In this case, there was a significant decrease in platelets during prior chemotherapy alone, but this almost completely improved naturally, and there was no clear worsening of adverse events when HVJ-E was administered subcutaneously with chemotherapy concurrently.

Regarding the progression of this case, combination therapy of CPT-11 and gemcitabine, including rechallenge of Cisplatin and Pemetrexed, was initiated approximately 42 months after the definitive diagnosis as the sixth line treatment without immune checkpoint inhibitor that was not developed and approved, the disease had advanced significantly even at the time of P-I registration. In the P-I clinical trial, disease progression was evaluated as NC. However, after the P-I clinical trial, the non-penetrating pericardial invasion progressed, and the resumption of chemotherapy was deemed necessary. During the administration of CPT-11, gemcitabine, and HVJ-E were administered subcutaneously, there was no significant disease progression. However, the disease progression of MPM led to severe pericardial effusion, resulting in severe dyspnea on effort. Consequently, the administration of HVJ-E was discontinued, and drainage was performed, and then pericardial fenestration was then performed [30], followed by chemotherapy with vinorelbine [31]. However, the patient was deceased 45.5 months after the definitive diagnosis, unfortunately.

4. Conclusions

After the P-I clinical trial with HVJ-E for inoperable chemotherapy-resistant MPM patients, we performed a novel therapeutic approach by administering HVJ-E and chemotherapy with CPT-11 and gemcitabine concurrently for the first time to a patient who had completed the P-I clinical trial.

This combination therapy did not result in any exacerbation of known adverse events or the emergence of new adverse events, thereby demonstrating its relative safety.

In the future, since combination therapy involving HVJ-E and chemotherapy is expected to demonstrate anti-tumor effects and no adverse events have been observed to become more severe, we would like to proceed with clinical trials of combination therapy involving HVJ-E and chemotherapy, or ICI for the early phase of MPM and other diseases.

5. References

1. Tsao AS, Wistuba I, Roth JA, Kindler HL. Malignant pleural mesothelioma. J Clin Oncol. 2009; 27:2081-2090.

2. Vogelzang NJ, Rusthoven JJ, Symanowski J *et al*. Phase III study of pemetrexed in combination with cisplatin versus cisplatin alone in patients with malignant pleural mesothelioma. J Clin Oncol. 2003; 21:2636-2644.
3. Okada M, Mimura T, Ohbayashi C, Sakuma T, Soejima T, Tsubota N. Radical surgery for malignant pleural mesothelioma: Results and prognosis. Interact Cardiovasc Thorac Surg. 2008; 7:102-106.
4. Aydin Y, Turkyilmaz A, Intepe YS, Eroglu A. Malignant pleural effusions: Appropriate treatment approaches. Eurasian J Med. 2009; 41:186-193.
5. de Perrot M, Wu L, Wu M, Cho BCJ. Radiotherapy for the treatment of malignant pleural mesothelioma. Lancet Oncol. 2017; 18:e532-e542.
6. Cinausero M, Rihawi K, Sperandi F, Melotti B, Ardizzoni A. Chemotherapy treatment in malignant pleural mesothelioma: A difficult history. J Thorac Dis. 2018; 10:S304-S310.
7. Nowak AK, Chin WL, Keam S, Cook A. Immune checkpoint inhibitor therapy for malignant pleural mesothelioma. Lung Cancer. 2021; 162:162-168.
8. Perrino M, De Vincenzo F, Cordua N, *et al*. Immunotherapy with immune checkpoint inhibitors and predictive biomarkers in malignant mesothelioma: Work still in progress. Front Immunol. 2023; 14:1121557.
9. Lopez-Castro R, Fuentes-Martin A, Medina Del Valle A, *et al*. Advances in Immunotherapy for Malignant Pleural Mesothelioma: From Emerging Strategies to Translational Insights. Open Respir Arch. 2024; 6:100323.
10. Sakura K, Sasai M, Funaki S, Shintani Y, Okumura M, Kaneda Y. Add-On Effect of Hemagglutinating Virus of Japan Envelope Combined with Chemotherapy or Immune Checkpoint Inhibitor against Malignant Pleural Mesothelioma: An *In Vivo* Study. Cancers (Basel). 2023; 15.
11. Nakajima T, Wada H, Yamauchi T, Kiyohara E, Kaneda Y. A Novel Therapy for Melanoma and Prostate Cancer Using a Non-Replicating Sendai Virus Particle (HVJ-E). Novel Gene Therapy Approaches. 2013; 13.
12. Sakura K, Kuroyama M, Shintani Y, *et al*. Dose-escalation, tolerability, and efficacy of intratumoral and subcutaneous injection of hemagglutinating virus of Japan envelope (HVJ-E) against chemotherapy-resistant malignant pleural mesothelioma: A clinical trial. Cancer Immunol Immunother. 2024; 73:243.
13. de Biasi AR, Villena-Vargas J, Adusumilli PS. Cisplatin-induced antitumor immunomodulation: A review of preclinical and clinical evidence. Clin Cancer Res. 2014; 20:5384-5391.
14. Suzuki E, Kapoor V, Jassar AS, Kaiser LR, Albelda SM. Gemcitabine selectively eliminates splenic Gr-1+/CD11b+ myeloid suppressor cells in tumor-bearing animals and enhances antitumor immune activity. Clin Cancer Res. 2005; 11:6713-6721.
15. Plate JM, Plate AE, Shott S, Bograd S, Harris JE. Effect of gemcitabine on immune cells in subjects with adenocarcinoma of the pancreas. Cancer Immunol Immunother. 2005; 54:915-925.
16. Iwai T, Sugimoto M, Wakita D, Yorozu K, Kurasawa M, Yamamoto K. Topoisomerase I inhibitor, irinotecan, depletes regulatory T cells and up-regulates MHC class I and PD-L1 expression, resulting in a supra-additive antitumor effect when combined with anti-PD-L1 antibodies. Oncotarget. 2018; 9:31411-31421.
17. Huang MY, Pan H, Liang YD, *et al*. Chemotherapeutic agent CPT-11 eliminates peritoneal resident macrophages by inducing apoptosis. Apoptosis. 2016; 21:130-142.
18. Soeda A, Morita-Hoshi Y, Makiyama H, *et al*. Regular dose of gemcitabine induces an increase in CD14+ monocytes and CD11c+ dendritic cells in patients with advanced pancreatic cancer. Jpn J Clin Oncol. 2009; 39:797-806.
19. Homma Y, Taniguchi K, Nakazawa M, *et al*. Changes in the immune cell population and cell proliferation in peripheral blood after gemcitabine-based chemotherapy for pancreatic cancer. Clin Transl Oncol. 2014; 16:330-335.
20. Dawson DW, Fernandez-Zapico ME. Gemcitabine Activates Natural Killer Cells to Attenuate Pancreatic Cancer Recurrence. Gastroenterology. 2016; 151:234-237.
21. Yin Y, Xie J, Peng F, *et al*. The topoisomerase inhibitor CPT-11 prevents the growth and metastasis of lung cancer cells in nude mice by inhibiting EGFR/MAPK signaling pathway. Heliyon. 2023; 9:e15805.
22. Kiyohara E, Tanemura A, Nishioka M, *et al*. Intratumoral injection of hemagglutinating virus of Japan-envelope vector yielded an antitumor effect for advanced melanoma: A phase I/IIa clinical study. Cancer Immunol Immunother. 2020; 69:1131-1140.
23. Kiyohara E, Tanemura A, Sakura K, *et al*. A phase I dose-escalation, safety/tolerability, and preliminary efficacy study of the intratumoral administration of GEN0101 in patients with advanced melanoma. Cancer Immunol Immunother. 2022; 71:2041-2049.
24. Fujita K, Nakai Y, Kawashima A, *et al*. Phase I/II clinical trial to assess safety and efficacy of intratumoral and subcutaneous injection of HVJ-E in castration-resistant prostate cancer patients. Cancer Gene Ther. 2017; 24:277-281.
25. Fujita K, Kato T, Hatano K, *et al*. Intratumoral and s.c. injection of inactivated hemagglutinating virus of Japan envelope (GEN0101) in metastatic castration-resistant prostate cancer. Cancer Sci. 2020; 111:1692-1698.
26. Koda YKK, Kijima T. Irinotecan and Gemcitabine as Second-Line Treatment in Patients with Malignant Pleural Mesothelioma following Platinum plus Pemetrexed Chemotherapy: A Retrospective Study. Oncology. 2021; 99(3):161-168.
27. Imataka H, Sekikawa T, Ichikawa W. The risk of adverse events of CPT- 11. Nihon Rinsho. 2016; 74:1847-1851.
28. Zheng Y, Dou Y, Duan L, *et al*. Using chemo-drugs or irradiation to break immune tolerance and facilitate immunotherapy in solid cancer. Cell Immunol. 2015; 294:54-59.
29. Zhang W, Wang Y, Jiang X, *et al*. Newly identified adverse events for gemcitabine using the Food and Drug Administration Adverse Event Reporting System. Expert Opin Drug Saf. 2024; 23:917-923.
30. Fujita T, Kawaguchi Y, Kataoka Y, Hanaoka J. Cardiac Hemangioma Producing Pericardial Effusion Detected on Thoracoscopic Pericardial Fenestration. Ann Thorac

Surg. 2022; 113:e359-e361.
31. Ost E, Illiger HJ. Vinorelbine in patients with malignant pleural mesothelioma-a phase II study. Strahlenther Onkol. 2001; 177:440-441.