

PD-1 Antibody Combined With Decitabine Is Effective in the Treatment of Refractory Peripheral T-cell Lymphoma Not Otherwise Specified: a Case Report

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Abstract

Background: Peripheral T-cell lymphoma not otherwise specified (PTCL-NOS) is a highly aggressive lymphoma with a poor response to chemotherapy, frequent relapses, low overall survival, and poor prognosis, and is the most common form of PTCL. For relapsed/refractory (R/R) PTCLs, the efficacy of traditional chemotherapy is even worse, so clinical trials and new drugs become their therapeutic hopes. Here, We report on a 43-year woman with refractory PTCL-NOS has a good response to PD-1 antibody combined with decitabine.

Case presentation: A 43-year-old woman with refractory PTCL-NOS, who has a poor efficacy in the first-line and second-line treatments, even the disease progresses after treatment with histone deacetylase inhibitors and proteasome inhibitors, however, has a good response to PD-1 antibody combined with decitabine. The patient got significant tumor regression and some of the masses even disappeared.

Conclusions: The PD-1 monoclonal antibody combined with decitabine may be a good choice to improve prognosis when used early if conventional first- and second-line regimens, histone deacetylase inhibitors, and proteasome inhibitors are ineffective.

Background

Peripheral T-cell lymphoma, not otherwise specified (PTCL-NOS) is a group of highly heterogeneous and aggressive malignant tumors[1], accounting for approximately 30–50% of PTCLs[2], usually occurring in middle-aged and elderly patients, with a male-to-female ratio of 1.5–1.9:1.0[3]. PTCL-NOS is characterized by systemic diseases with nodal or extranodal involvement, including lymph nodes, skin, liver, spleen, bone marrow, and peripheral blood. Nearly half of cases may have B symptoms at diagnosis, and may also encounter hemophagocytic syndrome characterized by fever, cytopenia, and spleen/liver enlargement[4]. There is no standard treatment regimen established for PTCL-NOS currently. The response to conventional chemotherapy is rather poor, and the 5-year median overall survival (OS) rate is usually less than 30%[5]. Besides, PTCL-NOS has no clear phenotype. Currently, the World Health Organization (WHO) classification of PTCL-NOS is based on its morphologic, immunophenotypic, cytogenetic and clinical features[6, 7]. In summary, no standard therapeutic regimens for PTCL-NOS were reported in previous studies, and there is a long way to go before we can conquer this hard nut. Here, we report a case of refractory PTCL-NOS, which has a poor efficacy in the first-line and second-line treatments, and even suffers disease progression with the treatment of histone deacetylase inhibitors and proteasome inhibitors. However, with the combined treatment of PD-1 antibody and decitabine, the patient got significant tumor regression and some of the masses even disappeared. Unfortunately, this patient developed IV degree of myelosuppression during remission and finally died of respiratory failure. In review of the previous studies of PTCL-NOS, we found that there existed no reports of such therapeutic strategy is effective in this disease. Therefore, we report this case for discussion and potential reference.

Case Presentation

A 43-year-old Chinese female inadvertently found multiple breast masses in April 2018, the larger one was about 2cm*3cm, self-conscious hard, clear border, good mobility, tenderness, no fever, itching, redness, etc. On June 6, 2018, she visited Chongqing Cancer Hospital & Chongqing University Cancer Hospital and a puncture biopsy of a right breast mass was performed. On June 21, the tissue examination revealed peripheral T-cell lymphoma, not otherwise specified (PTCL-NOS), and immunohistochemistry showed CD45 + Bcl-6 scattered + Bcl-2 scattered + CD5 + MUM-1 individual + Cyclin D1 + CD99dim + Fli-1 + Ki67 + > 80%, CD13- CD15- CD33- CD68(kp1)- CD68(PG-M1)- CD117- CD56- MPO- TdT- CK- Syn- CgA- Desmin- Myogenin- MyoD1- CK7- CD3- CD20- CD21- CD10- CD23- EBER- positive control + NSE-. On June 27th 18-F-fluorodeoxyglucose (FDG) positron emission tomography (PET) revealed that an abnormal FDG accumulation in bilateral neck, clavicular region, axillary fossa, upper limb, mediastinum, double hilar, abdominal wall, retroperitoneum, intestinal space, pelvic cavity, bilateral inguinal multiple lymphadenopathy, double lung, bilateral breast, stomach wall, left adrenal gland, spleen, occipital, under the chest wall multiple masses, and the whole body bone with high metabolic activity (SUVmax: 4.75–23.4), considering lymphoma involvement. On June 29, the first course of chemotherapy was started with P-CHOP (Pegaspargase 3750iu, epirubicin 80mg, cyclophosphamide 1.2g, vindesine 4mg, prednisone 500mg) and intrathecal injection, which cerebrospinal fluid was normal. On July 16th, the second course of HD-MTX(5g)and intrathecal injection were given. After a few days the masses reduced in size. On August 8th, the third course of treatment was given to P-CHOP and intrathecal injection. On August 23, the fourth course of HD-MTX5g was given and intrathecal injection. However, in the chemotherapy period, the masses increased again, and the disease progression (PD) was evaluated.

On September 5, 2018, the left breast mass biopsy was performed again and the pathological presentation showed that left breast mass conformed to peripheral T cell lymphoma with T-follicular helper cell phenotype, and immunohistochemistry were CD3 + CD20- CD21- ki-67 + 80% Bcl-2 + CD2p + CD5 + CD7 + CD4 + CD8 + CD56- GranzymB focal area + TIA-1 focal area + Perforin- TdT- PD-1 + CXCL-13- CD10- Bcl-6 + CD30- MUM- 1 scattered in + Cyclin D1 + 10% SOX11- CD23- CD117- CD33- CK- LCA+; Simultaneously, gastroscopy and biopsy showing pathological findings that stomach body conformed to peripheral T-cell lymphoma, NOS, and immunohistochemistry showed tumor cells CD3 ++ CD20- CD21- Bcl-2 + Ki-67 (about 30%+) CD10- Bcl - 6 + MUM-1 (scattered in small amount+) CD5 ++ CD23- CyclinD1 (scattered in small amount+) SOX11 (small stove+) CD30- c-myc (about 70%) TdT- PAX-5- p53 (about 20%) CD43++ κ chain (small stove+) λ chain- CD4 ++ CD8 ++ CD56- CD2 + CD7p+, EBER in situ hybridization-. On September 8 and October 1, respectively, the 5th and 6th courses of the GDP regimen (gemcitabine 1.65g*2d, cisplatin 120mg*2d, and dexamethasone 40mg*4d) were combined with histone deacetylase inhibitors - Chidamide. On October 30, the assessment again considered the progress of the disease (PD).

She admitted our hospital on November 7, 2018. Specialist examination: chronic illness, anemia, obvious pigmentation of the whole body, a large amount of scattered dandruff, superficial lymph nodes (submandibular, neck, armpit, trochle, groin, armpit) reaching the enlarged lymph nodes, which the texture is tough, fixed, obvious pain of inguinal lymph nodes. Both hearing weakened, the double breast touched multiple masses, with no tenderness, toughness, clear borders, good mobility, and mild edema in both lower limbs. Bone marrow cytology showed that bone marrow hyperplasia was active and lymphocyte morphology was abnormal, considering Non-Hodgkin's lymphoma bone marrow image and iron deficiency anemia (NHL-BMI, IDA). Skin biopsy pathology showed that pre-neck

V-zone skin consistent with peripheral T-cell lymphoma, tumor cell CD20- CD2 + CD3 + CD4 + CD5 + CD7 + CD8 + CD30- GranB- Ki-67 approximately 10% TCR recombinant+. As a result, combined with the patient history and examination, the diagnosis of refractory PTCL was established. So on November 9th and December 3rd, two courses of DEAD (doxorubicin liposome 20mg*3d, etoposide 150mg*3d, cytarabine 500mg*3d, dexamethasone 15mg*5d) were combined with Chidamide, which consciously the masses shrunk after chemotherapy, but the interval increased again. On December 18, the CLAG program (Cladribine 10 mg*5d, cytarabine 1g*4d, G-CSF 150ug*3d) was combined with thalidomide, and Simultaneously, the second generation gene sequencing showed: Notch1 and SOCS1 mutations.

At the beginning of January 2019, the patient's skin lesions, facial and limb edema were aggravated, and the finger joints were seen in the masses (Fig. 1), which the disease progression (PD) was evaluated. On January 14th, the PD regimen (bortezomib 2.27mg d1, 4, 8, 11 and dexamethasone 20mg d1-4, 8-11) was given, and edema slightly relieved on the 2nd day of treatment. But on January 18th, the whole body began to appear a large number of scattered masses, with highlighting the leather surface, hard, no tenderness, and progressively enlarging, which the largest one is located in the lower abdomen, about 3cm*5cm (Fig. 2), and the whole body appeared edema again. Therefore, we added bcl-2 inhibitors - venetoclax, and the disease still progressed after the end of the treatment.

On January 29th we tried PD-1 antibody - Carellidizumab (SHR-1210, 200mg, every 3 weeks) (Suzhou Shengdia Biomedical Co., Ltd.) combined with decitabine (25mg*5d). After treatment, the body masses were significantly reduced (Fig. 3), some of the masses disappeared, edema subsided, and evaluation of partial remission (PR). Unfortunately, before receiving the second cycle, the patient developed IV° myelosuppression and severe pulmonary infection. Despite the step up of antibiotic therapy and the addition of corticosteroids, the patient worsened, and eventually died of respiratory failure (Table 1).

Table 1
Treatment timescales

	Start time	therapy	Number of cycles	effect
1st	2018/6/29, 2018/7/16, 2018/8/8, 2018/8/23	P-CHOP (Pegaspargase, Epirubicin, Cyclophosphamide, Vindesine, Prednisone) HD-MTX P-CHOP HD-MTX	4	Stable disease; Progressive disease
2nd	2018/9/8, 2018/10/1	GDP (Gemcitabine, Cisplatin, Dexamethasone) + Chidamide(20mg, po, twice a week)	2	Progressive disease
3rd	2018/11/9, 2018/12/3	DEAD (Doxorubicin liposome, Etoposide, Cytarabine, Dexamethasone) + Chidamide(20mg, po., twice a week)	2	Progressive disease
4th	2018/12/18	CLAG (Cladribine, Cytarabine) + Thalidomide(25mg, po., daily)	1	Progressive disease
5th	2019/1/14	PD (Bortezomib, Dexamethasone) + Venetoclax	1	Progressive disease
6th	2019/1/29	Carellidizumab (200mg iv. every 3 weeks) + Decitabine (25mg iv. d2-6)	1	Partial response

Discussion

PTCL-NOS, a most common subgroup of PTCL, includes cases that do not correspond to any of the defined entities[8]. About 35%-45% of cases were diagnosed with B symptoms, including fever, systemic lymphadenopathy, fatigue, and unexplained weight loss. Sometimes, pruritus, eosinophilia, and hemophagocytic syndrome may be characteristic of this disease[9, 10]. Extranodal lesions can occur in approximately half of the cases, with the skin and gastrointestinal tract being the most frequently affected extranodal sites. Four prognostic index have been published to estimate survival in patients with PTCL-NOS, including age, serum LDH levels, performance status (PS), bone marrow involvement, Ann Arbor stage, extranodal involvement, thrombocytopenia, and tumor Ki-67 index[11, 12]. In addition, EBV and CCR4 positive are also poor prognostic factors[13, 14]. This patient had an ECOG score of 1 point, elevated LDH, bone marrow involvement, skin and gastrointestinal involvement, and EBV positive.

The best treatment options for PTCL-NOS are still controversial, due to its heterogeneity, complex clinical manifestations, difficult diagnosis, and lack of randomized controlled studies. The first-line chemotherapy regimen recommended by NCCN 2016 is CHOP, EPOCH, and Hyper-CVAD/MTX-Ara-C, and second-line options include DHAP, ESHAP, GDP, GND, GemOx, ICE, GVD, and new drugs such as pralatrexate, alemtuzumab, bortezomib, diltiazem, bendamustine, histone deacetylase inhibitor, PD-1/PDL-1 antibody, CD30 antibody - brentuximab vedotin, etc[15], or combined with chemotherapy[5]. Data on R/R PTCL will be presented separately, when available (Table 2). The patient's previous first-line and second-line treatment regimen was ineffective, even treated with the histone deacetylase inhibitor - Chidamide, the disease still progresses, which confirmed the diagnosis of relapsed/refractory PTCL-NOS, with stage IVb. In review with the patient's medical history and previous treatment regimens, different combinations of doxorubicin liposome, cladribine, bortezomib, thalidomide, etc. were had successively given, and the masses were progressively increased, which considering the treatment is ineffective. Even with new treatment regimens, relapsed/refractory PTCL-NOS patients still have poor survival outcomes, so there is an urgent need to develop more effective treatments for these patients[16, 17]. The US Food and Drug Administration (FDA) has approved brentuximab vedotin (BV) in 2011 for the treatment of relapsed PTCL patients with CD30 positive [5, 18]. Because of the patient's multiple biopsy immunohistochemistry showing CD30 negative, so BV was not considered.

Table 2
Selected Clinical Trial in Relapsed or Refractory PTCL patients, including PTCL-NOS

Treatment	Trial Phase	No. of patients	No. of PTCL-NOS	ORR	CR	Median PFS	Median OS	Toxicity	ClinicalTrials.gov Identifier	Reference
Romidepsin, Liposomal Doxorubicin	I	12	5 (42%)	27%	27%	2.1 months	17.5 months	grade 3/4 treatment-related hematologic AEs	N/A	33
Darinaparsin	I	14	10 (71.4%)	28.6%	7.1%	N/A	N/A	hematologic toxicities, nonhematologic toxicities (nausea, hepatic dysfunction and prolonged aPTT)	N/A	34
Bendamustine, Carboplatin, Dexamethasone	II	28	N/A	54%	29%	4.4 months	N/A	grade 3 or 4 neutropenia, thrombocytopenia, and anemia	NCT02424045	35
Pralatrexate	N/A	71	N/A	52%	N/A	4.8 months	18 months	stomatitis, anemia and alanine aminotransferase increase	NCT03349333	36
Alisertib	III	138	62 (45%)	33%	18%	115 days	14 months	anemia and neutropenia	NCT01482962	37
Romidepsin, Ifosfamide, Carboplatin, Etoposide	I	18	7(39%)	93%	80%	10 months	15 months	thrombocytopenia, anemia, neutropenia, fatigue, nausea/vomiting, infections, dyspnea and transaminitis	NCT01590732	38
Pralatrexate	I/II	25	12(48%)	45%	10%	150 days	not reached	mucositis, thrombocytopenia, liver function test abnormality, anemia and lymphopenia	NCT02013362	39
Romidepsin	N/A	130	69(53.1%)	24%	13%	5.4 months	18.2 months	thrombocytopenia	NCT00426764	40
Mogamulizumab	II	35	15(42.86%)	11.4%	2.86%	2.1 months	not reached	drug eruption, pyrexia, diarrhea, and pruritus	N/A	41
Gemcitabine, Romidepsin	II	20	10 (50 %)	30%	15%	2.5 months	18 months	thrombocytopenia, neutropenia, and anemia	NCT01822886	42
Panobinostat, Bortezomib	II	23	N/A	43%	21.5%	N/A	N/A	thrombocytopenia, neutropenia, diarrhoea, and asthenia or fatigue	NCT00901147	43
Chidamide	II	79	27(34%)	28%	14%	2.1 months	21.4 months	thrombocytopenia, leucopenia and neutropenia	N/A	44
Belinostat	II	120	77(64.2%)	25.8%	10.8%	1.6 months	7.9 months	anemia, thrombocytopenia, dyspnea, and neutropenia	N/A	45
Alisertib	II	37	13(35%)	30%	7%	3 months	8 months	neutropenia, anemia, thrombocytopenia, febrile neutropenia, mucositis, and rash	NCT01466881	46

In recent years, blocking immune checkpoints is considered an important breakthrough in cancer treatment, especially PD-1 inhibitors in anti-tumor therapy. The anti-PD-1 monoclonal antibody specifically binds to the PD-1 molecule on the surface of T cells, thereby blocking the PD-1/Programmed Cell Death-1 (PD-L1) pathway, which leading to tumor immune tolerance, re-activating the anti-tumor activity of lymphocytes, thereby achieving the purpose of treating tumors[19]. As far as lymphoma is concerned, PD-1 antibody has a significant effect on classic Hodgkin's lymphoma[20]. Kwong et al. reported the results of PD-1 antibody - Pembrolizumab in the treatment of R/R ENKTL patients who failed asparaginase therapy, showing that the overall response rate (ORR) was

100% (7/7), and the CR rate was 71.4% (5/7)[21]. Barta SK, et al. have shown that PD-1 monoclonal antibody - Pembrolizumab exhibits modest single-agent activity in relapsed or refractory T-cell lymphoma, mainly through AKT inhibition of T-cell receptor-mediated signal transduction[22]. Several studies have also confirmed the presence of abnormally hypermethylation in T-cell lymphoma and their cell lines, often occurring in the promoter region of tumor suppressor genes (eg: P15INK4B, SHP-1, P53) and leading to silencing of the gene.

Recently, recurrent mutations in epigenetic modified genes have been found in PTCL-NOS. Importantly, studies by Ji MM, et al. provide clinical evidence that histone-modified gene mutations, particularly those involved in histone methylation and acetylation, which is significantly associated with tumor chemoresistance and disease progression in PTCL-NOS[23]. Decitabine is a nucleoside analogue. Phosphatiated decitabine is involved in DNA synthesis, and then covalently binds to DNA methyltransferase to inhibit its activity, resulting in hypomethylation of DNA and activation of tumor suppressor genes, thereby which cause cell differentiation or apoptosis [24, 25].

It has been reported that DNA methylation of new organisms promotes T cell failure and limits anti-PD-1 immunotherapy, while methylation inhibition can enhance T cell regeneration mediated by PD-1 blockade[26, 27]. Theoretically, decitabine and anti-PD-1 antibodies play a synergistic effect to restore immune surveillance. Nevertheless, in a small retrospective analysis, a high CR rate of PD-1 inhibitors was observed in several patients with relapsed/refractory cHL who had received epigenetic therapy[28]. Whether the combination of anti-PD-1 antibody and decitabine can enhance the anti-tumor T cell lymphoma effects has not been reported. Combined with the review of relevant literature, this patient still chooses decitabine combined with carrelizumab for treatment, and the effect is also definite. The results had shown that the combination of decitabine and carrelizumab is safe, and the CR rate for patients with relapsed/refractory cHL is very high[29]. Since immune-based therapy requires appropriate immune activation, the epigenetic modifier decitabine can promote T cell activation and enhance the effectiveness and duration of the clinical response of anti-PD-1 antibodies.

The patient was found to be positive for PD-1 in immunohistochemistry, so we tried PD-1 antibody combined with decitabine. After treatment, the whole body mass was significantly reduced, and some of the masses disappeared, which was considered effective. By destroying the combination of PD-1 and PD-L1 on tumors or other immunosuppressive cells, PD-1 blockers can restore the activity of tired T cells. However, compared with effector and memory T cells, exhausted T cells have unique epigenetic properties and will not be remodeled by PD-1 blockade, which may limit the long-lasting anti-tumor ability of anti-PD-1 antibodies[30]. Low-dose decitabine may change the epigenetic status of tumors and immune cells. Although decitabine alone is not sufficient to treat advanced solid tumors, low-dose decitabine can enhance T cell activity, promote the infiltration of CD8 + and CD4 + T cells, increase the sensitivity of chemotherapy drugs and broaden the T cell receptor library in peripheral blood[31, 32]. Therefore, the enhanced anti-tumor response of decitabine combined with PD-1 blockers may be caused by multiple mechanisms. Although this patient's disease has been effectively relieved, we expect allogeneic hematopoietic stem cell transplantation after better control of the disease. Unfortunately, due to multiple strong chemotherapy, the patient developed IV degree of myelosuppression during the course of the disease and eventually died of respiratory failure.

Conclusion

In summary, this case report on the diagnosis of relapsed/refractory PTCL-NOS is rare. Survival outcomes in patients with progressed/relapsed PTCL-NOS were still poor, with no significant changes even with new treatment regimens. It is necessary to enter the clinical trial at an early stage and combined the new drugs, which after the disease is controlled, allogeneic hematopoietic stem cell transplantation can be performed as soon as possible to improve survival. Reviewing the course of the patient, PD-1 monoclonal antibody combined with decitabine may be a good choice and improve prognosis with early using when conventional first- and second-line regimens, histone deacetylase inhibitors, and proteasome inhibitors et al. are ineffective. Further research is necessary to evaluate this novel treatment option.

Abbreviations

FDG: fluorodeoxyglucose; FDG-PET: 18-F-fluorodeoxyglucose-positron emission tomography; HD-MTX: high dose of methotrexate; IDA: iron-deficiency anemia; NHL-BMI: non-hodgkin's lymphoma bone marrow image; PTCL-NOS: peripheral T-cell lymphoma, not otherwise specified; OS: overall survival; PD: disease progression; PS: performance status; PD-1/ PD-L1: programmed cell death protein 1 and its ligand; BV: brentuximab vedotin.

Declarations

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Authors' contributions

HX drafted the manuscript. WQ administered chemotherapy. LX, WK, YHJ are involved in the medical treatment and took care of the patient's follow-up. ZC provided academic advice. ZX contributed to manuscript revision. All authors read and approved the final manuscript.

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Availability of data and materials

All data generated or analyzed are included in this published article

Ethics approval and consent to participate

All data were collected anonymously and with patient's consent. All procedures in this study were approved by the Ethics Committee of the Second Affiliated Hospital of Army Medical University.

Consent for publication

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

Competing interests

The authors declare that they have no competing interests.

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Figures



Figure 1

skin lesions, facial and limb edema, and the finger joints were seen in the masses.



Figure 2

PTCL-NOS involvement in skin causing skin masses seen on the limbs, face, and abdomen, etc. PTCL-NOS: peripheral T cell lymphoma, not otherwise specified.



Figure 3
skin of the limbs, face, and abdomen masses were significantly reduced, and some of the masses disappeared. a, on the 4th day after PD-1 mAb combined with decitabine treatment. b, on the 16th day after PD-1 mAb combined with decitabine treatment.