Hyperprogression on anti-PD-1 treatment. Is subsequent therapy feasible? A case report and review of the literature

Jan Skacel, Bohuslav Melichar, Beatrice Mohelnikova-Duchonova, Radmila Lemstrova

Background. Hyperprogressive disease (HPD) is a new phenomenon that has emerged in the immunotherapy era. HPD is defined as a rapid tumour growth with detrimental effect on the patient condition and disease course. The management and treatment following HPD is not defined. We present here the case report of patient with HPD and review of the literature on putative mechanisms of HPD and following disease management.

Methods and Results. A 60-year old male patient with metastatic melanoma was indicated for systemic treatment with anti-programmed cell death (PD)-1 antibody. Rapid tumour growth and detrimental effect on the patient general condition after administration of a single dose of anti-PD-1 antibody met the criteria of HPD. The patient underwent the second line taxane-based chemotherapy with good tolerance and disease stabilization. The third line treatment with anti- cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) antibody ipilimumab was well tolerated and resulted in partial response. Re-challenge with anti-CTLA-4 antibody was feasible, but only with a modest clinical effect.

Conclusion. Prompt recognition of HPD and administration of salvage chemotherapy with taxane-based regimens may be crucial. HPD is rarely observed with ipilimumab treatment. Administration of ipilimumab as well as an ipilimumab re-challenge are feasible after HPD on anti-PD-1 antibodies. Investigation of new predictive biomarkers of HPD is warranted as well as new agents that potentiate the immune response in patients affected with this insidious complication.

Key words: hyperprogressive disease, nivolumab, ipilimumab, melanoma, paclitaxel

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Department of Oncology, Faculty of Medicine and Dentistry, Palacky University Olomouc and University Hospital Olomouc, I.P. Pavlova 6, 779 00 Olomouc, Czech Republic
Corresponding author: Radmila Lemstrova, e-mail: lemstrovi@gmail.com

INTRODUCTION

The advent of immune checkpoint inhibitors (ICI) has resulted in a radical change in the therapy of malignant tumours. The treatment with programmed cell death 1 (PD-1) and cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) inhibitors has prolonged the overall survival (OS) of patients with a range of solid tumours, including metastatic melanoma, renal cell carcinoma, non-small cell lung cancer (NSCLC), urothelial carcinoma or Merkel cell carcinoma. An extensive search for predictive and prognostic biomarkers of the antitumor immune response has followed the growing ICI treatment experience. Expression of PD-L1, presence of tumour infiltrating lymphocytes (TIL), tumour mutational burden (TMB), i.e. the number of somatic mutations per DNA mega base (Mb), and microsatellite instability have emerged as predictive biomarkers. However, the utilization of these biomarkers in clinical practise has some serious limitations. A new phenomenon called hyperprogression or hyperprogressive disease (HPD) has emerged recently in association with immunotherapy. HPD is defined as a rapid tumour growth with detrimental effect on the patient condition and disease course. Studies use different criteria for defining rapid tumour growth. Some authors define HPD as an increase of more than 50% of the tumour burden within less than 2 months since the treatment initiation and doubled pace time compared to the pre-treatment status[1] or simply a tumour progression of more than 50% at the time of the first evaluation[2]. The mechanism of this phenomenon remains elusive. The management and treatment following HPD is not defined. The prompt use of chemotherapy such as taxanes has been suggested.

We present here the case report of patient with HPD including subsequent management along with a review of the literature on the potential biomarkers of HPD.

CASE REPORT

A 60-year old male patient presented with a 1 cm large pigmented lesion on the right arm. Histological examination confirmed metastasis of melanoma. A positron emission tomography- computed tomography (PET/CT) scan demonstrated metastases in 3 right axillary lymph nodes 11 mm in diameter as well as metastatic lesions in the second lumbar vertebra and in the right femur. (Fig. 1A) The patient had no comorbidities and had a history of surgery for nodular melanoma on the right arm, Breslow 7.5 mm, Clark V, and with ulceration a year earlier. An exploration of the right axilla had been performed for a

Table 1. HDP studies.

Study	Cancer type	HPD definition	No. of evaluated patients	No. of HPD patiens	HPD biomarkers	Methods
Kim et al. (2019)	NSCLC	TTF < 2 months, ≥2-fold increase in TGR, TGK ≥ 2, RECIST1.1 progression	263	TTF: 98/263 (37.3%), TGR: 54/263 (20.5%), TGK: 55/263 (20.9%)	Low frequencies of $CCR7^{-}CD45RA^{-}$ $CD8^{+}$ T cells High frequencies of $TIGIT^{+}$ in $PD\text{-}1^{+}CD8^{+}$ T cells	Flow cytometry
Kamanda et al. (2019)	AGC	TTF < 2 months, ≥2-fold increase in TGR and > 2-fold increase in progression speed	36	4/36 (11.1%)	Increased $PD\text{-}1^{+}$ Treg cells ($FoxP3highCD45RA^{-}CD4^{+}$T cells) in tumor tissues	IHC, flow cytometry
Kato et al. (2017)	Multiple cancer types	TTF < 2 months, > 50% increase in TMB and > 2-fold increase in progression pace	155	6/155 (4%)	MDM2/4 family amplification – 4/6 (67%) EGFR aberrations – 2/10 (20%)	NGS
Koyama et al. (2016)	NSCLC	HPD not stated Accelerated tumor growth – tumor growth to 120% of the original tumour after initial treatment response	2	2/2 (100%)	Increased expression of TIM-3 in CD4 and CD8 T cells from PD-1 resistant tumour	mRNAseq, flow cytometry, ELISA
Lo Russo et al. (2019)	NSCLC	TTF < 2 months, ≥2-fold increase in TGR, at least two new lesions in an organ, spread to a new organ,, deteoriation of ECOG ≥ 2, at least three of the above criteria and RECIST 1.1 progression	152	39/152 (25.7%)	Tumor infiltration by M2-like $CD163^{+}CD33^{+}PD\text{-}L1^{+}$ clustered epithelioid macrophages, Low PD-L1 expression in tumor cells	IHC, flow cytometry

TGR, Tumor growth rate; TGK, Tumor growth kinetics; TTF, Time to treatment failure; CI, Confidence interval; HR, Hazard ratio; OS; Overall survival; AGC, Advanced gastric cancer; IHC, Imunohistochemistry; TMB, Tumor mutational burden; NGS, Next generatiom sequencing; OR, Odds ratio; ECOG, Eastern Cooperative Oncology Group

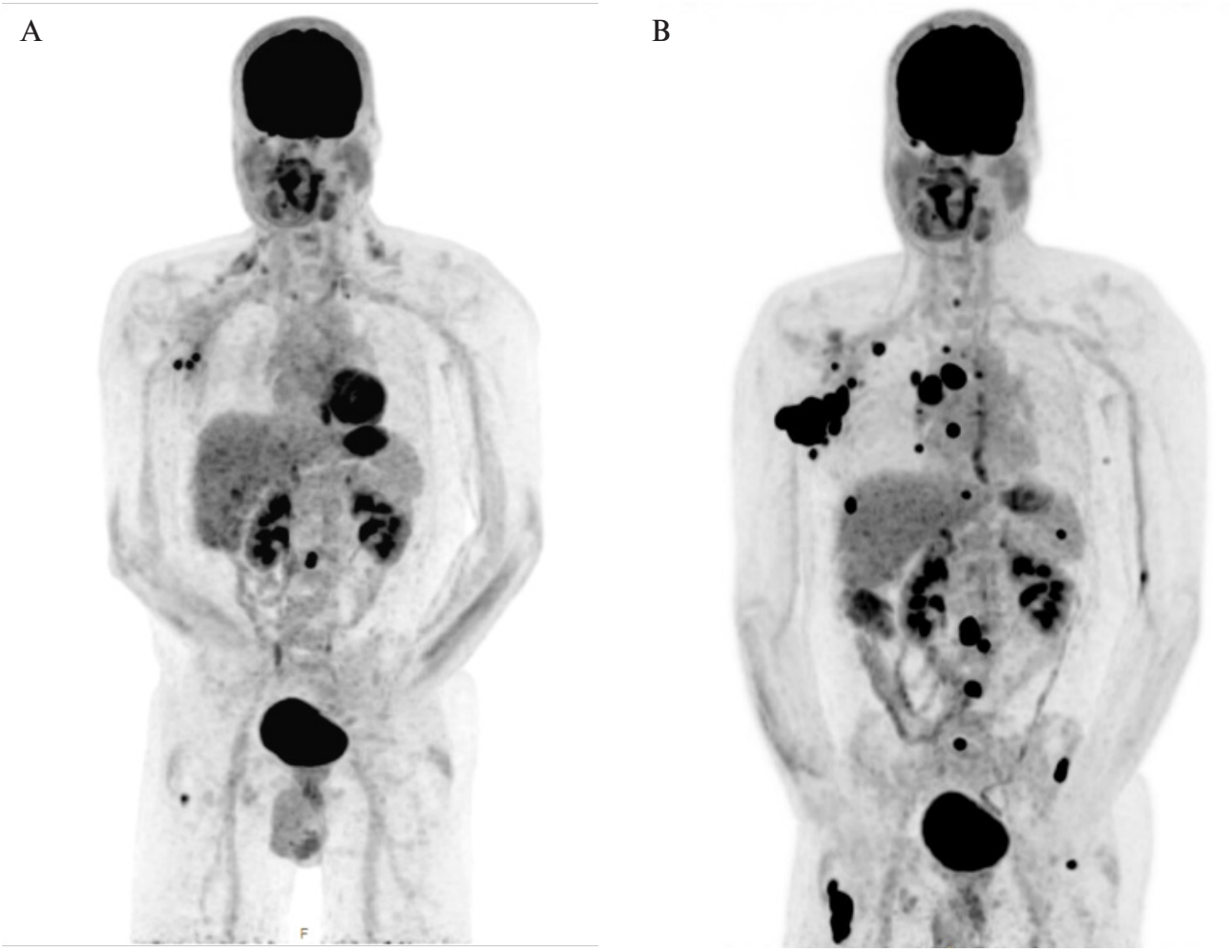

Fig. 1. A. Extent of the disease before the inicialization of the anti-PD 1 treatment. B. Extent of the disease after 8 weeks of treatment with anti-PD-1 antibody.

suspicious lymph node with a histological confirmation of a single lymph node metastasis with extracapsular growth out of 16 lymph nodes examined. The patient had undergone radiotherapy to the right axilla with the total target dose of 48 Gy.

A mutation analysis performed before the initiation of the metastatic disease therapy revealed BRAF wild type phenotype. The blood count and biochemistry values, including lactate dehydrogenase (LDH), were within the physiological range. The patient started first line immunotherapy with single agent pembrolizumab 200 mg intravenously (iv) every three weeks. The World Health Organisation (WHO) performance status was 0. However, a week after the administration of the first pembrolizumab dose the patient presented with multiple black cutaneous nodules in his right axilla and the right pectoral region. The nodules were between 5 and 10 mm in diameter. The patient also complained about weakness, loss of appetite and back pain. Two additional doses of pembrolizumab were administered with no improvement of the condition. The PET/CT scan performed 8 weeks after the start of the treatment showed lesions of the right axillary lymph nodes with invasion to the surrounding soft tissues of the right arm and to the infraclavicular lymph nodes 50 x 29 mm in size, metastasis in the right parasternal, precarinal and the right hilar lymph nodes up to 25 mm in diameter, 3 subcutaneous lesions in the pectoral region of 10 mm in size, and multiple osteolytic lesions in the thoracic and lumbar vertebrae, sacrum, in the left iliac bone, both femurs, sternum, in the 8th right rib and the 10th left rib. (Fig. 1B)

The patient underwent additional palliative radiotherapy of the painful lesion in the right axilla with source-axis distance (SAD) technique and a total target dose of 20 Gy.

Subsequently, second line chemotherapy with the combination of paclitaxel 80 mg/m^2 and carboplatin 2 mg /area under the curve (AUC) weekly i.v. was started. The condition of the patient improved, he could stop using analgesics, the appetite was restored resulting in a weight gain of 5 kg, and he could walk long distances again. However, within 3 months the condition began to deteriorate again. Repeat PET/CT scan confirmed progression of the disease, including the cutaneous metastasis of the right arm and axilla, mediastinal lymph nodes, skeletal metastases as well as new lesions in both adrenal glands and the abdominal wall.

The 3rd line of the systemic treatment with 4 triweekly doses of iv ipilimumab 3 mg/kg was initiated. The treatment was well tolerated. Areas of vitiligo around the meta-

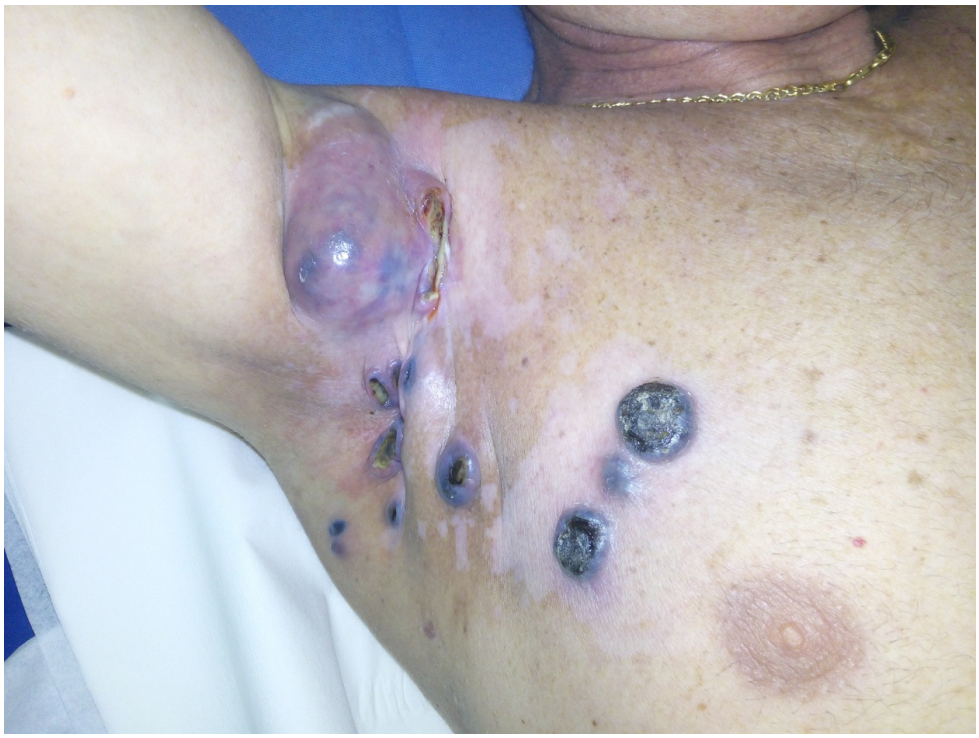

Fig. 2. Vitiligo associated with the 3rd line systemic treatment with anti-CTLA-4 antibody.

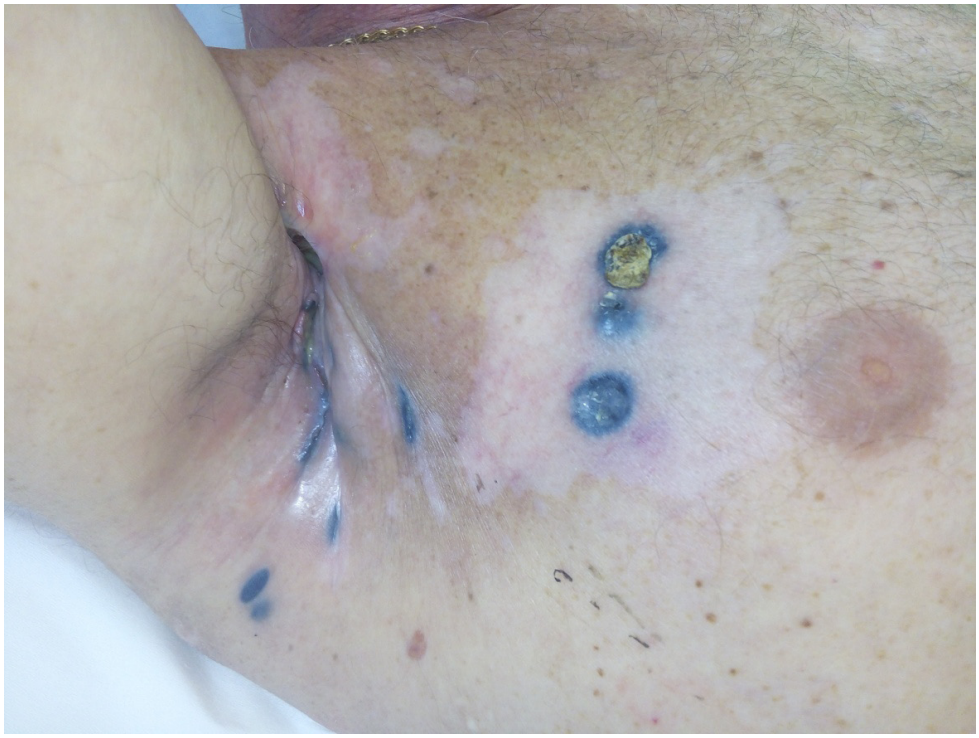

Fig. 3. Treatment response to the 3rd line of anti-CTLA-4 antibody.

static cutaneous lesions were noticed. (Fig. 2) A partial regression of the cutaneous metastasis of the right axilla and the pectoral region was observed (Fig. 3), and subsequently confirmed by PET/CT scan. The osteolytic metastases remained stable. The patient began to feel well again, and the treatment response lasted 10 months. Subsequently, the patient began to complain about back pain in the region of the thoracic vertebral column, and underwent palliative radiotherapy of the osteolytic lesion of the 9th thoracic vertebra to a total target lesion dose of 20 Gy. A new PET/CT scan confirmed disease progression in the right axilla, mediastinal lymph nodes, both pulmonary hilar regions, multiple osteolytic lesions of the thoracic and lumbar vertebrae, sacrum, left iliac bone,

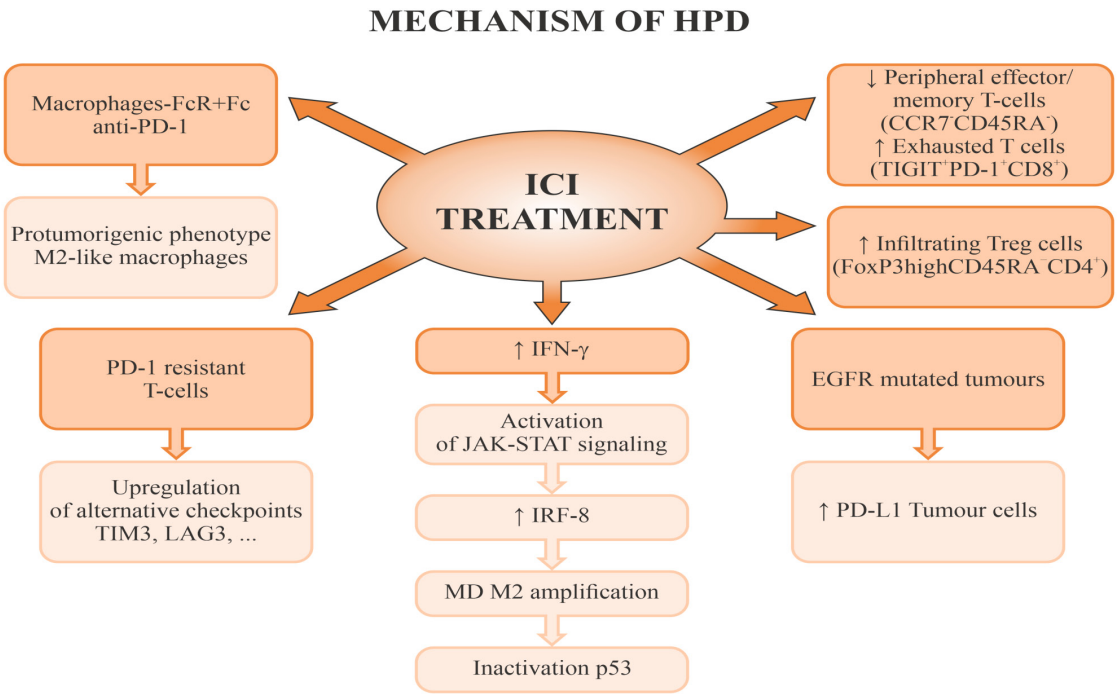

Fig. 4. Diagram of mechanism of hyperprogressive disease (HPD).
ICI, Immune checkpoin inhibitors; IFN- γ, Interferon-γ; EGFR, Epidermal growth factor receptor; PD -1, Programmed cell death protein 1; PD-L1, Programmed death ligand 1; Tregs, Regulatory T cells; IRF-8, Interferon regulatory factor; MDM2, Mouse double minute 2 homolog.

metastasis of the left adrenal gland and demonstrated multiple metastases of the small intestine. A suspicious dense lesion was noted in the brain frontal region 7 mm in diameter that was asymptomatic. The patient underwent a re-challenge with 4 doses of ipilimumab (3 mg/kg) triweekly with no apparent response. The patient had an emergency surgery for ileus due to the progression of the small intestine metastasis in the jejunal loop which increased to 12 cm. Subsequently, the condition of the patient deteriorated rapidly and palliative hospice care was initiated. The patient died 22 months after the initiation of the metastatic disease treatment. Mutational analysis with next generation sequencing (NGS) and multiplex ligation–dependent probe amplification (MLPA) revealed no pathogenic variant in the genes of hereditary syndromes analysed (ATM, APC, BARD1, BRCA1, BRCA2, BRIP1, CDH1, CHEK2, EPCAM, MLH1, MSH2, MSH6, MUTYH, NBN, PALB2, PMS2, PTEN, RAD50, RAD51C, RAD51D, STK11, and TP53).

DISCUSSION

The present case of a patient with rapid tumour growth following the administration of a single dose of anti-PD-1 treatment resulting in detrimental effects on the general condition meets the criteria of HPD(ref.[1,2]). The mechanism(s) of HPD remain elusive, although multiple theories have been proposed that are outlined below.

TUMOUR CELL-INTRINSIC MECHANISMS

Genomic alterations

Potential genomic biomarkers associated with HPD disease during anti-PD1 and anti-CTLA-4 therapy have been extensively studied. There is growing evidence of an association between mouse double minute 2 homolog (MDM2) family amplification or epidermal growth factor receptor (EGFR) aberrations and HPD in various cancer types. MDM2 acts as a ubiquitin ligase, being responsible for adding ubiquitin moieties to the p53 tumour protein. As p53 expression increases, MDM2 blocks directly the p53 transactivation domain and targets the p53 protein itself, resulting in ubiquitin-dependent proteasome degradation and inactivation of the p53 protein[3,4]. The immune checkpoint inhibitors (ICI) treatment, i.e. inhibition of the PD-1 pathway, could cause an increase of interferon-γ (IFN-γ) levels[5], which may stimulate the Janus kinase/signal transducer and activator of transcription (JAK-STAT) pathway[6], leading to overexpression of the interferon regulatory factor (IRF-8) (ref.[7]). Subsequently, IRF-8 binds to the MDM2 promoter inducing the MDM2 amplification[8,9]. Loss of p53 activity is one of the key factors in oncogenesis. EGFR plays a role in the cell growth, proliferation and differentiation through activation of many cellular signalling pathways[10]. A possible explanation of EGFR induced HPD is that EGFR mutation leads to PD-L1 up regulation on cancer cells which results in T cell deactivation[11]. Kato et al. evaluated tumour samples of 155 patients with next generation sequencing (NGS). MDM2/4 amplification was observed in 6 patients, in-

cluding 4 patients with HPD on anti-PD1/PDL1 monotherapy. EGFR was altered in 10 patients, and HPD was observed in 2 of these 10 patients. However, 35 patients who received an anti-CTLA-4 treatment (alone or combined with antiPD1/PDL1) were significantly less likely to have HPD(ref.[1]). The authors suggest that genomic profiling may help to identify the patients at risk for HPD associated with anti-PD1 treatment.

TUMOUR CELL-EXTRINSIC MECHANISMS

a. Circulating peripheral T cells

Pre-existing antitumor immunity is essential for the regression of tumour and predicts the patient response to the immune checkpoint blockade. Kim et al. analyzed the frequencies of effector/memory subtypes in $CD8^+$T lymphocytes in patients with NSCLC treated with PD-1 blockade. Lower frequencies of effector/memory cell subtypes $CCR7^-CD45RA^-$ predicted HPD on the treatment with PD-1 inhibitors[12]. The authors suggest that anti-PD-1 treatment may enhance activation-induced cell death resulting in HPD. A higher frequency of severely exhausted $CD8^+$ T cells -T cell immunoglobulin and immunoreceptor tyrosin-based inhibition motif (ITIM) domain ($TIGIT^+PD\text{-}1^+CD8^+$T cells) was observed in patients with HPD compared to the non-HPD patients leading to the conclusion that responsiveness to PD-1/PD-L1 reinvigoration is limited to the less exhausted subsets of the tumour-reactive T cells.

b. Immunosuppressive microenvironment of the tumour

Upregulation of alternative immune checkpoints

Treatment with anti-PD1 antibodies may be accompanied by an upregulation of alternative checkpoints, such as lymphocyte activation gene 3 (LAG3), T cell immunoglobulin and ITIM domain (TIGIT) and, most notably, the T-cell immunoglobulin mucin-3 (TIM-3). Koyama et al. analyzed T cell populations in the microenvironment of genetically engineered lung carcinoma in immunocompetent mice and performed mRNA sequencing of anti-PD1-treatment resistant versus untreated tumours. The treatment resistance was defined as a tumour growth of > 120% of the original tumour size after initial therapeutic response evaluated by MRI. The authors found an increased expression of genes associated with T cell suppressive function, in particular TIM-3, LAG-3 and PD-1. A control analysis of the expression at the protein level, flow cytometry of CD4 and CD8 T cells was performed. Higher levels of TIM-3, LAG-3, and CTLA-4 were observed in both CD4 and CD8 T cells from PD-1 resistant compared to the untreated tumours, but only the difference in TIM3 expression was significant. Increased TIM-3 expression was detected only in the tumour–bearing lungs, but not in the other tissues. The positivity of TIM-3 positively correlated with the duration of the PD-1 blockade. An interesting observation is that no upregulation of TIM-3 was noted during CTLA-4 blockade. These results were confirmed on tumour samples of two patients with lung adenocarcinoma. Upregulation of the T cell suppressive alternative checkpoints in anti-PD-1 resistant tumours may lead to accelerated growth[13].

M2-like macrophages

Potential interaction of tumour associated macrophages and anti-PD-1 antibody was studied by Lo Russo et al. who observed HPD in 39 out of 152 patients with NSCLC treated with immune checkpoint inhibitors. HPD was associated with M2-like ($CD163^+CD33^+PD\text{-}L1^+$ clustered epithelial macrophages) infiltration. To confirm the association between the M2-like macrophages and HPD after anti-PD-1 therapy immunodeficient mouse xenograft models were studied. In the mouse xenografts derived from HPD tumour samples, infiltration with M2-like macrophages was increased following anti-PD-1 antibody treatment leading to accelerated tumour growth. It was speculated that binding of the macrophage-FcR (CD32B) and the Fc domain of the anti-PD-1 antibody may activate a signalling cascade that promotes functional reprogramming of these cells toward a more aggressive pro-tumorigenic phenotype leading to HPD in subset of patients with distinctive immune and genetic profile[14].

Regulatory T cells

Kamada et al. compared the gastric cancer tissues before and after anti-PD1 treatment and reported that anti-PD1 treatment increased the tumour-infiltrating proliferative effector Tregs ($FoxP3^{high}CD45RA^-CD4^+$T cells) in HPD patients in contrast to the reduction in non-HPD patients. These tumour-infiltrating effector Tregs are highly suppressive and express PD-1 at much higher levels than circulating effector Treg cells. The authors conclude that PD-1 blockade may enhance the proliferation of these highly suppressive $PD\text{-}1^+$ effector Treg cells and inhibit the antitumor immunity. The presence of actively proliferating tumour infiltrating $PD\text{-}1^+$ effector Treg cells is strongly associated with HPD (ref.[15]).

On the other hand, in patients with advanced-stage cervical cancer an increased number of tumour infiltrating $FOXp3^+$Treg cells was shown to be associated with positive clinical outcome. The PD-1/PD-L1 signalling plays a critical role in host-cancer immune equilibrium affecting the dynamics of Tregs[16]. Moreover, Tregs homeostasis may be affected by the newly identified LKB1 tumour suppressive gene. In mice models the Lkb1-deficient $Foxp3^+$ Tregs showed upregulation of PD-1 expression. PD-1 blockade can reinvigorate Tregs that leads to suppression of Th2 (T helper 2) mediated immune responses[17]. Th2 are effector cells and produce cytokines such as IL-4, IL-5, IL-6, IL-9 and IL-13 which activate proliferation of B cells, macrophages and production of immunoglobulins[18]. Suppression of Th2 may cause the immune escape and accelerated tumour growth.

Immunosuppressive cytokines

Cytokines and other checkpoint mediators are also important factors that affect the adaptive immune response. Lamichhane et al. found that PD1/PD-L1 blockade induces increased IL-10 secretion by tumour-infiltrating dendritic cells (DCs) (ref.[19]). The increased IL 10 secre-

tion results in further upregulation of PD-L1 expression on DCs that facilitates the immune escape. PD1 inhibition may also induce overexpression of IL-10 receptors on tumour-specific $CD8^+$ T cells as reported in patients with advanced melanoma making them more susceptible to immune suppression by IL-10 (ref.[20]). IFNγ probably plays a role in the immune suppression as well[21]. IFNγ is an important activator of macrophages and inducer of major histocompatibility complex class II molecule expression[22]. Nevertheless, IFN-γ produced by tumour infiltrating-lymphocytes may upregulate PD-L1 expression in tumour cells[23]. Kao et al. reported that IFN-γ upregulates PD-L1 mRNA expression in malignant pleural mesothelioma (MPM) cells due to the activation of the interferon regulatory factor 1 (IRF1) transcription factor[24]. Tumour cell-derived PD-L1 is able to bind to the PD-1 receptor and to trigger pro-apoptotic signals into activated T cells and further contribute to an immunosuppressive microenvironment in MPM. Moreover, it has been recently shown in NSCLC patients that circulating PD-L1 might interfere with the efficacy of anti-PD-L1 antibodies by trapping them. Thus, PD-L1 might also disrupt the anti-PD-L1 antibody-dependent cellular cytotoxicity (ADCC) of MPM cells[25]. Therefore, persistent activation of IFNγ signalling might, paradoxically, promote cancer immunoediting and the emergence of resistance to ICI agents. This suggest a potentially immunosuppressive role of persistent IFNγ production.

Currently there is no specific biomarker or subset of biomarkers that would predict the risk of HPD in an individual patient. More studies on different cellular subpopulations in both peripheral blood and the tumour microenviroment, expression of immune checkpoints with the cognate ligands and cytokine secretion are warranted.

Despite the HPD on anti-PD-1 treatment, the presented patient had a good response to the second line chemotherapy with paclitaxel and carboplatin combination. A small retrospective analysis showed increased chemotherapy response rate after the administration of anti-PD-1, principally in the treatment of NSCLC. Schvartsman et al. report overall response rate (ORR) of 39% (11/28 patients) to a single agent chemotherapy in the 3rd line setting after progression on anti-PD1 treatment of advanced NSCLC (ref.[26]). This ORR in the 3rd line setting was similar to the ORR to the first line platinum-based combination chemotherapy of 37% (10/27 patients). Synergism between immunotherapy and cytotoxic chemotherapy has been hypothesized. Chemotherapy increases neoantigen expression and antigen cross-presentation, causes a disruption of tumour stroma resulting in increased immune cell penetration and upregulation of death receptors on the tumour cells. Moreover, cytotoxic drugs may eliminate myeloid-derived suppressor cells/regulatory T- cells and enhance the immune response[27-31]. A restored balance of the immunostimulatory and immunosuppressive cells after chemotherapy may have caused the favourable treatment response even after previous progression on anti-PD-1 agent.

Several cytotoxic agents have been used in the treatment of metastatic melanoma including dacarbazine, temozolomide, fotemustine, paclitaxel and carboplatin, as single agents or in combinations, with the response rate ranging between 5% and 29% (ref.[32,33]). The taxane-based regimens seem to be a reasonable treatment option after HPD. Taxanes inhibit the microtubule dynamics leading to mitotic block and arrest of the cell cycle in the G2/M phase triggering apoptosis of the fast proliferating cells. However, the development of secondary resistance represents a major obstacle for the improvement in the treatment response and patient survival.

HPD has rarely been documented in patients treated with a single-agent CTLA-4 inhibitor. In the present patient with metastatic melanoma and a history of HPD on anti-PD-1 treatment the decision has been made to administer anti-CTLA4 antibody ipilimumab in the third line of therapy. The patient experienced a partial response of the cutaneous and lymph nodes metastases lasting for 10 months and tolerated the treatment well without any serious adverse events.

The consideration of the 4th line of the treatment was very challenging. There is some evidence of treatment response to re-challenge of anti-CTLA-4 antibodies. Reschke et al. published a pooled data analysis of 182 patients pre-treated with ipilimumab[34] and reported a mean disease control rate of 50.9% and ORR of 20.4% to the ipilimumab re-challenge. The authors assume too that patients who responded to the initial checkpoint inhibition will also respond to a re-challenge. However, response rates are lower after re-challenge compared to initial checkpoint therapy. Ipilimumab re-challenge was indicated in the fourth line of the treatment in the present patient who underwent the re-challenge without any severe toxicity. However, the response was of limited duration, the patient had to undergo an emergency surgery due to local complications associated with the growth of the tumour lesions, and the subsequent condition of the patient did not allow administration of any further antitumour therapy.

CONCLUSION

HPD is a new phenomenon that has emerged in the immunotherapy era. Patients with HPD on anti-PD1 therapy have a poor prognosis. Prompt recognition of HPD and administration of salvage chemotherapy may be crucial. Chemotherapy with taxane-based regimens appears to be active. HPD is rarely observed with anti-CTLA-4 treatment. Administration of anti-CTLA-4 antibodies as well as an anti-CTLA-4 re-challenge are feasible after HPD on anti-PD-1. However, the treatment response to anti-CTLA-4 re-challenge in pre-treated patients is very limited. Investigation of new predictive biomarkers of HPD is crucial for the identification of patients at risk of HPD as well as new agents potentiating immune response in patients affected with this insidious complication.

Search strategy and selection criteria

Our research strategy was aimed at evaluating studies on potential mechanisms of HPD. Scientific articles

from 1990 to 2021 were searched using the PubMed database. The search terms used included “hyperprogressive disease”, “immune checkpoint inhibitors”, “anti-PD-1”, “anti-PD-L1”, “anti-CTLA-4”, “melanoma”. Only English language papers were reviewed.

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