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Principles of Standardized Diagnosis and Treatment of Immune Checkpoint Inhibitors (ICIs) and Analysis of Legal Liability for Treatment-Related Tumor Hyperprogression (HPD) Under Chinese Law

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Abstract

Immunotherapy, led by immune checkpoint inhibitors, has reshaped the landscape of tumor treatment, achieving long-acting drug responses in some patients with advanced malignancies, but not all patients can benefit from immunotherapy. In addition to primary drug-resistant patients, we cannot ignore hyperprogressive patients whose disease is accelerated instead after the use of immune checkpoint inhibitors, which are rare but often have a very poor prognosis and are prone to disputes. The mechanism of hyperprogression is still unknown, but not unknown, and some genetic mutations and biomarkers have been shown to be associated with a higher risk of hyperprogression. Clinicians should stratify patients with reference to markers and risk mutations to screen effective patients and inform them of the corresponding risks of immune checkpoint inhibitor therapy to ensure that patients make a fully informed choice of immunotherapy. Comply with evidence-based medical guidelines, standardize the use of medication, and timely monitor and intervene in related adverse events and hyperprogression. Under Chinese law, violation of the principles of diagnosis and treatment is subject to liability, except for those caused by the patient himself, such as backline treatment and sympathetic drug administration.

Keywords: immunotherapy, immune checkpoint inhibitors, tumor hyperprogression, standardized treatment, legal liability

1. Introduction

Different from chemotherapy and molecular targeted therapy, which directly kill tumor cells, immunotherapy acts on the human immune system, activating immune cells and lifting immunosuppression, and acts on the tumor immune microenvironment (TME), prompting the immune cells to kill the tumor, thus realizing long-term tumor remission. Immunotherapy, led by immune checkpoint inhibitors (ICIs) targeting PD-1, PDL-1, and CTLA4, has completely changed the landscape of tumor treatment, with certain efficacy observed in pan-tumor types, and long-term survival of patients with long-lasting response to the drugs.

It is important to note that not all patients will benefit from immune checkpoint inhibitors. Unlike chemotherapy and targeted therapies, in addition to primary resistance, immunotherapy is often associated with a variety of atypical response patterns, including long-lasting response, isolated response, delayed response, pseudoprogression, and hyperprogression[1]. Depending on the response to immune checkpoint inhibitors, the prognosis of patients varies. Of the many atypical response patterns, only the hyperprogressive pattern does not benefit from treatment, but rather results in a worse prognosis as a result of treatment, with an incidence of approximately 4%-30% reported in the literature[2]. In contrast to the side effects of conventional oncological treatments such as chemotherapy, targeted drugs and radiation therapy, immunotherapy-induced hyperprogression is the result of the drug treatment itself altering the natural course of the disease and promoting accelerated tumor growth, whereas in the former case, it is the effect of the toxicity of the treatment on the normal cells of the human body.

Although the application of immune checkpoint inhibitors brings life to some patients with advanced tumors, it is not a "panacea". Under the boom of drug research and development, clinical trials and clinical application of

immune checkpoint inhibitors for pan-tumor tumors, a small number of hyper-progressive patients seem to be selectively ignored, but such patients often have extremely poor prognosis and are prone to doctor-patient disputes. At the same time, the risk of hyperprogression of immune checkpoint inhibitors in patients with early-stage, resectable tumors in the context of advancing the number of immunotherapy lines is worthy of consideration. In order to prevent the resulting doctor-patient disputes and promote the benign development of doctor-patient relations, it is necessary to determine the basic principles of diagnosis and treatment of immune checkpoint inhibitors to ensure that clinicians standardize the use of medication, thereby avoiding the legal risks and clarifying the legal responsibilities when necessary.

2. Analysis of the Current Status of Immune Checkpoint Inhibitors in the Field of Tumor Therapy and the Associated Risk of Hyper-Progression

2.1 Analysis of the Current Development and Clinical Status of Immune Checkpoint Inhibitors

Immunotherapy, broadly defined, includes therapies such as immune checkpoint inhibitor therapies (ICIs), tumor-infiltrating lymphocyte therapies (TILs), chimeric antigen receptor T cell therapies (CAR-T), and natural killer T cell therapies (NKT), with immune checkpoint inhibitors being the most widely used[3][4][5]. Immune checkpoint inhibitors are antibodies designed to inhibit immune checkpoints by restoring the immune system's recognition of tumor cells and inhibiting immune escape, thus killing tumor cells, among which programmed death receptor protein 1 (PD-1), programmed death receptor ligand 1 (PDL-1) and cytotoxic T-lymphocyte-associated protein (CTLA-4) are the most widely used targets. CTLA-4) are the most mature targets[6].

The remarkable efficacy demonstrated in pan-tumor randomized controlled trials and in the real world has set off a frenzy in the development, launch and application of immune checkpoint inhibitors. On the R&D front, domestic and international pharmaceutical companies have stepped up their efforts to compete for market share. All major pharmaceutical companies have set up multi-pipeline R&D on immune checkpoint inhibitors, including improvement of drugs with original targets, such as SHR-1210 (novel PD-1) and Quavonlimab (novel CTLA-4); development of new immune checkpoints, such as Relatlimab (LAG-3), Cobolimab (TIM-3) and Ociperlimab (TIGIT), among others; and multispecific antibodies that can target multiple checkpoints, such as KN046 (PD-1/CTLA-4), Tebotelimab (LAG-3/PD-1), and rilvegostomig (PD-1/TIGIT).

In terms of clinical trial setup, as of today, there are 5,683 single-agent or combination clinical trials for PD-1/PDL-1 inhibitors alone underway worldwide. Compared with 2017, the total number of clinical trials over the past five years has increased by 278% year-on-year, with monoclonal antibody clinical trials that are temporarily in the clinical development stage without FDA approval accounting for 29% of the total number of clinical trials. Of the 4,897 active clinical trials, 4,062, or 83%, combined PD1/PDL-1 inhibitors with targeted therapies, chemotherapy, and radiation therapy, etc. 35 bispecific antibodies are in clinical trials, of which 21 are in Phase I, 10 are in Phase II, and 4 are in Phase III[7].

In terms of drug application, more and more single-agent or combination regimens of pan-tumor immune checkpoint inhibitors are recommended by domestic and international evidence-based medical guidelines, and the level of evidence-based medicine is constantly rising. In terms of the number of treatment lines, the use of immune checkpoint inhibitors is also advancing, from backline treatment to first-line treatment, and even to neoadjuvant and adjuvant (perioperative) treatment. Major pharmaceutical companies have also joined forces with foundations to launch various drug subsidy policies, which have greatly improved drug accessibility and led to the widespread use of immune checkpoint inhibitors in clinical practice. Regimens using immune checkpoint inhibitors, including PD-1, either alone or in combination, seem to have become the right thing to do in oncology treatment.

The development and over-treatment of immune checkpoint inhibitors has become a serious public health problem[8] , and it seems that immune checkpoint inhibitors have not reproduced the stunning data from clinical trials in several real-world studies (RWS), and their efficacy has been greatly reduced[9][10][11]. In addition to the minority of primary drug-resistant patients, it is important to note that there are also hyperprogressive patients whose tumors have accelerated as a result of the use of immune checkpoint inhibitors. Under the general trend of immunotherapy, these few patients do not seem to have attracted enough attention, and these patients also tend to have dramatically shorter survival and a very poor prognosis.

2.2 Tumor Hyperprogression due to Immune Checkpoint Inhibitors

In addition to non-responding primary drug-resistant patients, multiple atypical response patterns are often seen with the use of immune checkpoint inhibitors, including long-lasting response, isolated response, delayed response, pseudo-progression, and hyper-progression. The different response patterns reflect the different strengths of anti-tumor immunity triggered by the drug, and the prognosis of progression varies. Long-acting responses generate

immune memory, which signals the possibility of a "cure"; isolated responses, delayed responses, and pseudoprogression can also benefit from treatment, to varying degrees; and hyper-progressive patterns accelerate tumor progression. Hyper-Progressive Disease, HPD) as a concept. Hyper-Progressive Disease (HPD) was first introduced at the European Society of Medical Oncology (ESMO) conference in 2016.

According to the Response Evaluation of Solid Tumors (RECIST) 1.1 criteria, a significant increase in the diameter of a tumor lesion, or the appearance of a new lesion, was defined as disease progression (PD) on radiographic imaging. Immunocheckpoint inhibitor-associated tumor hyperprogression, on the other hand, is defined as a rapid increase in the rate of tumor progression induced by immunocheckpoint inhibitor therapy, and its criteria are mainly based on two parameters, tumor growth rate (TGR) or tumor growth kinetics (TGK). Currently, the criteria for tumor hyperprogression are generally considered to be both: (1) progression occurs within 2 months (2) increase in baseline tumor load by more than 50% (3) acceleration of tumor growth kinetics by more than twice the original rate (TGR/TGK>2)[12].

In clinical practice, radiologic imaging data prior to the baseline level are often difficult to obtain, resulting in the inability to calculate TGK or TGR. Some scholars have proposed Fast progression, i.e., the maximum diameter of the target lesion exceeding 50% within 6 weeks of treatment initiation (as distinguished from the general PD criterion of 30%), or death due to tumor progression within 12 weeks as an alternative indicator for assessing hyperprogression[13] . Time to treatment failure (TTF) shorter than 2 months has also been proposed as an alternative indicator of hyperprogression[14]. However, it is undeniable that the alternative index cannot dynamically reflect the impact of immunotherapy on tumor growth, and it is difficult to distinguish it from the natural course of the disease, so it has certain limitations.

The mechanism by which immunotherapy leads to tumor hyperprogression remains unknown, with some studies suggesting that it may be related to off-target effects, and exacerbation of T-cell depletion[15]. Some molecular level mutations and markers, such as MDM2 amplification and CCND1 amplification, have also been found to be associated with a higher risk of tumor hyperprogression[16]. Tumor hyperprogression associated with immune checkpoint inhibitors has been observed in pan-tumors with an incidence of approximately 4-30% reported in the literature[17]. In the past era of chemotherapy and targeted therapies, the so-called "hyperprogression" phenomenon was rare, mostly reported as an isolated case, and difficult to distinguish from the natural course of the tumor. It was not until the introduction of immune checkpoint inhibitors that the phenomenon of tumor hyperprogression caused by immune checkpoint inhibitors was systematically observed and reported, and gradually gained attention. The prognosis of patients with hyperprogressive tumors is extremely poor, and the survival period is greatly shortened. In the era of immunotherapy, how to avoid the risk of treatment-related hyperprogression is a serious problem and a new challenge that has to be faced in clinical work.

3. Standardized Diagnosis and Treatment: Principles of Treatment with Immune Checkpoint Inhibitors

3.1 Effective Screening of Patients for Potential Benefit

Not all patients can benefit from immune checkpoint inhibitors, and ineffective immunotherapy increases patients' immune-related adverse events (irAEs) while risking tumor hyperprogression. Therefore, it is crucial to rely on well-documented biomarkers at the molecular level for precision therapy, to effectively screen for the benefit of immune checkpoint inhibitors, and to avoid over-treatment of ineffective populations. With the development of high-throughput sequencing (NGS) and multiplex immunohistochemistry technologies, the understanding of tumor microlevels, such as tumor immune microenvironment (TME), has gradually deepened. After the introduction of immune checkpoint inhibitors, some efficacy predictors have been reported.

Several studies have shown[18-20] that high PDL-1 expression, high tumor mutation load (TMB), carriage of high microsatellite instability (MSI-H), or defective mismatch repair genes (dMMR) are associated with better efficacy of immune checkpoint inhibitors[21, 22]. In addition to the above predictive markers, which have been well studied and well-documented, there are also predictive markers such as immune cell subsets (e.g., CD4+T, CD8+T, Tregs, etc.), gene mutations (e.g., BRAF, PTEN, CCND1, etc.), and HLA heterozygous deletion (LOH), which are not as well-documented as the indicators such as TMB, but they can also serve as references to clinicians for stratifying and selecting patients. [23, 24] The evidence is not as strong as that of TMB, but it can be used as a reference for clinicians to stratify patients.

Of course, the available predictive markers are not as good as they could be in terms of both sensitivity and specificity. Taking PDL-1 expression as an example, several studies have shown that even patients with low PDL-1 expression may benefit from immunotherapy[25-27]. The limitations of any single marker make it difficult to effectively screen for benefit. It is necessary for clinicians to combine the test and the patient's specific condition with various predictive markers of efficacy to comprehensively evaluate the patient's physical ability and tumor

immune status, and to inform the patient of the risks and disadvantages of immunotherapy, including the potential benefits, according to the patient's specific situation. For patients with "cold tumors" with poor tumor immune microenvironment, it is prudent to choose immune checkpoint inhibitors or combination therapies when necessary, in order to achieve precise treatment and avoid ineffective treatments that increase risks.

3.2 Hazard Stratification of Patients by Reference to Risk Mutations and Markers

The mechanisms of tumor hyperprogression due to immune checkpoint inhibitors remain unknown, but not unknown, and available studies suggest that a number of molecular-level mutations and markers are associated with a higher risk of hyperprogression. Markers known to be associated with higher hyperprogression findings include advanced age (65+years), elevated serum lactate dehydrogenase (LDH) levels, multiple metastases, local recurrence, MDM2/MDM4 amplification, CNKNA/B deletion, CCND1 amplification, and EGFR mutations[28]. Similar to the benefit indicators of immunotherapy, the above risk indicators of hyperprogression are only indicative and are not absolute contraindications to the use of immune checkpoints, and the correlation between the various markers and the risk of hyperprogression is not exactly the same.

Taking EGFR mutation as an example, the study showed that EGFR mutation-positive patients were more likely to develop treatment-related tumor hyperprogression compared to EGFR mutation-negative (wild-type) patients treated with PD1 inhibitors, with an incidence of 16.3% vs 1.9%, OR=8.36 (P=0.02), suggesting the informative significance of EGFR mutation in the prediction of hyperprogression by immunotherapy, . In addition, several basic studies have supported the mechanism of immune hyperprogression at the molecular level in patients with EGFR mutations[29-31]. In a real-world study, up to 44.8% of non-small cell patients (NSCLC) with EGFR mutations showed immunotherapy-related hyperprogression[32]. All of the above studies suggest the value of EGFR mutations as a high-risk predictor of hyperprogression with immunotherapy. Other predictors, such as the advanced age factor, which was associated with a higher risk of hyperprogression in the study by Champiat[33] et al, were not supported by several other studies[34, 35].

Different predictive markers have different clinical significance and different levels of evidence, which need to be further investigated. In addition, as with the benefit markers of immunotherapy, there are limitations in the detection of a single predictive marker of hyperprogression. Clinicians should stratify patients' risk according to their physical status, specific disease, and predictors of hyperprogression. For patients with high-risk markers with a high level of evidence-based medicine, such as EGFR mutation, or patients with multiple risk markers at the same time, clinicians should inform them of the corresponding risk of hyperprogression, use immune checkpoint inhibitors with caution, and reasonably screen the use of drugs. Literature reports that combination therapy can reduce the risk of hyperprogression associated with immunotherapy, suggesting that clinicians can combine other therapies when necessary based on following the guidelines, and at the same time closely monitor the occurrence of side effects and hyperprogression[36].

3.3 Ensure that Patients Make Fully Informed Choices about Immunotherapy

Informed Consent (Informed Consent) system from the common law, also known as informed consent, explaining consent, as its name suggests, that is, on the basis of fully informed consent decision-making. As a basic principle of modern medical treatment, in the doctor-patient relationship, the medical party has the obligation to inform, and the corresponding patient has the right to be fully informed, and has the right to consent to medical activities on the basis of fully informed decision-making[37-41]. In the doctor-patient relationship, the content of informed consent includes the patient's condition, medical measures, the medical risks of the corresponding measures and alternative medical programs, etc., and the target of informed consent is, in principle, the patient himself or herself, and in the case where it is not appropriate to inform the patient, his or her close relatives may also be the target of informed consent. Informed consent system built on the basis of natural persons on their own personal and health of the complete self-determination, medical activities, the fulfillment of the obligation to inform the medical practitioner, can prevent the original infringement of personal injury behavior (such as surgery, intubation and checkups, etc.) of the illegality of the law. At the same time, the extent of informed consent varies according to the type of medical treatment, for example, in the case of emergency medical treatment, informed consent may be exempted to a certain extent.[42-44]. In terms of empirical law, China's informed consent system is mainly found in the Civil Code and the Physicians Law, in addition to sporadic references in such scattered norms as the Regulations on the Administration of Rural Doctors' Practices, the Work System of Hospitals, the Regulations on the Administration of Medical Institutions, and the Regulations on Human Organ Transplants.

With the increase of life expectancy and the aging of the population, the incidence of malignant tumors is increasing year by year, and oncology treatment has become one of the common clinical medical activities, of which antitumor drug therapy is an important part of clinical oncology treatment. Common antitumor drugs include

cytotoxic drugs, targeted drugs and immune checkpoint inhibitors. In recent years, although antitumor drugs have developed rapidly, the prominent toxic side effects should not be underestimated. In tumor drug treatment, informed consent is also an important system to avoid legal risks and prevent disputes between doctors and patients, and the fulfillment of the duty of informed consent can prevent the illegality of seemingly personal torts (e.g., injection of cytotoxic drugs). Clinically, the obligation of informed consent is often fulfilled by the signing of an informed consent form. Grossman et al. [45] conducted a quantitative study of 137 informed consent forms and found that in oncology treatment, informed consent forms are still characterized by poor readability, and thus verbal explanations are also an important part of the obligation of informed consent. In antitumor drug therapy, the information should include the possible benefits, risks, adverse effects and symptomatic management measures of antitumor drugs, and based on this, the patient's consent to the treatment plan should be obtained.

Specifically, immune checkpoint inhibitors have their own unique pharmacological properties and mechanisms, and their risks, adverse side effects and symptomatic management measures are very different from those of previous cytotoxic or targeted drugs. As mentioned before, not all patients can benefit from immune checkpoint inhibitors in terms of efficacy, and some biomarkers, such as PDL1 expression, have certain significance. Meanwhile, in terms of adverse effects, unlike the liver, kidney, blood and reproductive toxicity of common cytotoxic drugs, the common side effects of immune checkpoint inhibitors are immune-related adverse effects (irAEs), including hypothyroidism, pituitary gland inflammation, and immune-related hepatitis, pneumonitis, and enterocolitis, etc. 1/2 low-grade adverse effects are mostly controllable, and the use of the drug is not affected by the treatment of the symptoms, 3/4 high-grade adverse effects can even be life-threatening, while 3/4 high-grade adverse effects can even be life-threatening, and 3/5 high-grade adverse effects can even be life-threatening. High-grade adverse reactions can even be life-threatening and require hormonal control and termination of drug therapy[46] . In addition, especially for patients with high-risk markers such as EGFR mutations or multiple markers associated with the risk of hyperprogression, the risk of hyperprogression associated with immune checkpoint inhibitors should not be ignored. All of the above should be communicated to the patient by the clinician to ensure that the patient is fully informed of his/her condition, the benefits and risks of the drug, and to make the choice of immunotherapy.

3.4 Standardization of Medication Based on Evidence-Based Medical Treatment Guidelines

Medicine has moved from traditional empirical medicine to modern evidence-based medicine, and clinical diagnostic and treatment activities are gradually moving towards "evidence-based and homogeneous", of which medical diagnostic and treatment standardization guidelines are the foundation. Medical diagnosis and treatment standardization guidelines are accumulated on the basis of a large amount of evidence-based medicine, and they are the consensus norms guiding clinical diagnosis and treatment in the medical field, and their normative basis is reflected in the unity of external form norms (norms of formulation and implementation) and internal substance legitimacy (in line with scientific laws and medical ethics).[47]

The status of different diagnostic and treatment protocols varies according to the quality of their evidence-based medical grade, authority and degree of consensus. For example, the tumor diagnosis and treatment guidelines formulated by the Health and Welfare Commission, the anti-tumor drug regulations in the National Pharmacopoeia, and the instructions for use of drugs undoubtedly have the highest level of effectiveness. Secondly, there are the diagnosis and treatment guidelines and expert consensus formulated by professional associations such as the Chinese Medical Association and the Chinese Society of Clinical Oncology, such as the CSCO guidelines, as well as the tumor guidelines formulated by famous professional associations in the global medical field, such as the U.S. NCCN oncology diagnosis and treatment guidelines and the European ESMO oncology diagnosis and treatment guidelines. Finally, there are medical textbooks, academic monographs and professional papers. It should be pointed out that under the system of evidence-based medicine, high-level diagnostic and therapeutic specifications often require higher accumulation of evidence and quality of evidence, i.e., high-level diagnostic and therapeutic specifications often have the problem of lagging, which requires a large amount of high-quality evidence, and this also lays down the space for the system of over-indication/superspecification of medication.

Article 23 (2) of the Law of the People's Republic of China on Physicians stipulates that clinicians should follow clinical diagnosis and treatment guidelines, and comply with clinical technical codes of practice and codes of medical ethics. However, similar to the standard, standardization law has mandatory standards and recommended standards, as a product of scientific experience, the standard[48], its nature is not a law, and does not have the mandatory nature of the law, authorized by the authorities and laws and regulations citing the standard, given the standard to the mandatory effect[49]. Medical diagnosis and treatment standard guideline is also not a law, does not have mandatory effect itself, laws and regulations refer to the diagnosis and treatment guideline, the promulgation of the authority or authorized authority makes the diagnosis and treatment guideline has mandatory

effect, clinicians need to standardize the use of drugs on the basis of diagnosis and treatment guideline. Of course, as stated in the Declaration of Helsinki, when there is no existing effective prophylactic, diagnostic, or therapeutic method for treating a patient, and if the physician feels that there is a hope of saving a life, regaining health, or relieving suffering, then the physician, with the patient's informed consent, should use the as-yet-unproven or new prophylactic or therapeutic measures without restriction, diagnostic and therapeutic measures. The ultimate goal of medicine is to cure disease and restore health, and all medical ethics serve this purpose, thus giving rise to the system of overdescription, which is recognized in comparative law[50, 51], and the issue of overindication/overdescription will be discussed later.

4. Timely Monitoring and Intervention for Immunization-Related Adverse Events and Associated Tumor Hyperprogression

The prognosis of treatment-related tumor hyperprogression with immune checkpoint inhibitors is extremely poor, and once tumor hyperprogression occurs, the survival of the patient will be drastically shortened. Of course, in addition to treatment-associated tumor hyperprogression, the more common side effect of immune checkpoint inhibitors remains the occurrence of immune-related adverse events (irAEs) caused by them. Common immune-related IRAEs include hypothyroidism, pituitary gland inflammation, and immune-related hepatitis, pneumonia, and enteritis, etc. Low-grade 1/2 IRAEs are mostly controllable and do not affect the continued use of the drug after symptomatic treatment, while high-grade 3/4 IRAEs, such as immune-related pneumonitis, can be life-threatening and require hormonal control and may lead to permanent termination of the immune checkpoint inhibitor therapy and initiation of an alternative medical regimen. Alternative medicine program[52].

In terms of monitoring and intervention for hyperprogression, medication should be closely monitored, especially in patients with poor physical status, the presence of high-risk markers, or the presence of multiple markers associated with the risk of hyperprogression. If the occurrence of immunotherapy-associated hyperprogression is monitored, the treatment of immune checkpoint inhibitors should be stopped immediately, no other immune checkpoint inhibitor treatment should be used, and glucocorticoids or other immunosuppressants should be applied for symptomatic treatment. Other alternative treatment regimens should be initiated when the patient's vital signs are stable, and chemotherapy may be an effective remedy after the occurrence of immunotherapy-related hyperprogression as reported in the literature[53, 54].

To summarize, after patients are fully informed of their own conditions, treatment benefits and risks and choose immune checkpoint inhibitor therapy, especially for patients with poor physical condition or the presence of predictive markers associated with the risk of hyperprogression, clinicians need to closely monitor the patient's condition during the medication period, dynamically assess the patient's status, and strive for early detection of immune-related adverse events and hyperprogression, and early intervention, and timely and appropriate treatment. The clinicians should try to detect and intervene early for immune-related adverse events and hyperprogression, treat the symptoms in a timely manner, stop the ineffective or even harmful therapeutic regimen, and replace it with other effective regimens to maximize the prognosis of patients.

5. Analysis of Legal Liability for Immunotherapy-Related Tumor Hyperprogression

5.1 Liability Prerequisites: Distinguishing Tumor Hyperprogression from the Natural Course of the Disease

Oncological diseases have their natural course, for tumors with poor biological behavior and high degree of malignancy, even after active anti-tumor therapy, they are still prone to poor local tumor control, recurrence or even distant metastasis, i.e., according to Response Evaluation of Solid Tumors (RECIST) 1.1 criteria, on radiological imaging, significant increase in the diameter of the tumor foci or the appearance of new foci is defined as disease progression (PD). The distinction between immunotherapy-related tumor hyperprogression and progression of the natural course of the disease is a prerequisite for the assumption of the relevant legal liability, and there is no question of assuming the relevant liability for hyperprogression if the tumor progression is due to the natural course of the disease.

As mentioned before, immune checkpoint inhibitor-associated tumor hyperprogression is defined as a rapid increase in the rate of tumor progression induced by immune checkpoint inhibitor therapy, which is based on two parameters, tumor growth rate (TGR) or tumor growth kinetics (TGK), and its criteria are generally considered to require the simultaneous fulfillment of the following conditions: (1) progression occurring within 2 months (2) baseline tumor load increase of more than 50% (3) accelerated tumor growth kinetics of more than twice the original (TGR/TGK>2)[55] . However, in clinical practice, radiographic information prior to the baseline level is often difficult to obtain, resulting in the inability to calculate TGK or TGR.

Some scholars have proposed Fast progression, i.e., maximum diameter of the target lesion exceeding 50% within 6 weeks of treatment initiation (as opposed to 30% for RECIST criteria for PD), or death due to tumor progression within 12 weeks, as an alternative indicator for assessing hyperprogression[56]. Time to treatment failure (TTF) shorter than 2 months has also been proposed as a surrogate for assessing hyperprogression[57]. Compared with TGR and TGK, the alternative index cannot dynamically reflect the impact of immunotherapy on tumor growth, and it is difficult to distinguish it from the natural course of the disease, so it has certain limitations. In addition, immunotherapy is often associated with a variety of atypical response patterns, including long-lasting response, isolated response, delayed response, pseudo-progression, and hyper-progression[58], which should be differentiated from hyper-progression. Pseudo-progression refers to the increase in tumor diameter or the appearance of new foci initially observed after the use of immunocheckpoint inhibitors, which meets the RECIST criteria for progression. RECIST criteria for progression, but after adherence to treatment, the tumor is found to shrink or even disappear. Pseudo-progression is also considered to be a benefit scenario for immunotherapy[59, 60]. Pseudoprogression may also exceed 50% of the maximum single diameter of the tumor. Based on imaging evaluation alone, there is a risk of mistaking pseudoprogression for hyperprogression when using alternative indicators, and pathological biopsy has some significance in identifying pseudoprogression.

5.2 Liability for Hyperprogression of Tumors in the Absence of a Duty of Adequate Information

Informed consent is an important principle-based system of modern medical treatment, and China's Civil Code, Physicians Law and Human Organ Transplant Regulations all provide for an informed consent system in different ways and to different extents, requiring clinicians to fully explain the specific condition, medical treatment and risks to the patient or his/her close family members, and to ensure that the patient or his/her close family members make a decision to consent on the basis of being fully informed. If a medical practitioner fails to fulfill his or her duty to inform the patient, violating the patient's right to make autonomous decisions about his or her body and health, he or she may constitute a medical tort of informing the patient of his or her medical condition and is liable for damages. The scope of compensation is "damage caused by failure to inform", i.e. the part of damage that has a causal relationship between the failure to inform and the result of the damage, which is generally regarded as not different from the usual scope of medical damages.[61]

Specifically on the issue of immune checkpoint inhibitor use and risk of hyperprogression, as mentioned earlier, the mechanisms of tumor hyperprogression due to immune checkpoint inhibitors, although still unknown, are still in evidence, with a number of molecular-level mutations and markers associated with a higher risk of hyperprogression. Markers known to be associated with higher findings of hyperprogression include advanced age (over 65 years), elevated serum lactate dehydrogenase (LDH) levels, multiple metastases, local recurrence, MDM2/MDM4 amplification, CNKNA/B deletion, CCND1 amplification, and EGFR mutations. The above risk indicators for hyperprogression are only indicative and are not absolute contraindications to the use of immune checkpoints, and the correlation between various markers and the risk of hyperprogression is not identical. For patients with predictive markers of hyperprogression, especially those with high quality evidence-based markers such as EGFR mutations, or those with multiple markers associated with the risk of hyperprogression, clinicians should fully inform patients of the possible risk of hyperprogression associated with the use of immune checkpoint inhibitors. For patients who obviously have risk markers related to hyperprogression, if the medical practitioner gives immune checkpoint inhibitor treatment without fully informing the patient of the obligation, resulting in hyperprogression of immunotherapy-related tumors, it will constitute a notification-type medical infringement, and will be liable for compensation.

With regard to the exclusion of liability, if the medical practitioner informs the patient of the risk of hyperprogression, and the patient insists on immunocheckpoint inhibitor treatment even though the patient is aware of the presence of risk markers related to hyperprogression, the medical practitioner is excluded from liability for informing the patient of the tort in the event of treatment-related hyperprogression. Meanwhile, the identification of some molecular risk markers, such as MDM2/MDM4 amplification, CNKNA/B deletion, CCND1 amplification, and EGFR mutation, should be based on the premise of relevant molecular pathology tests (e.g., immunohistochemistry, Fish and NGS sequencing, etc.). If the patient refuses to undergo the relevant molecular pathology tests for his or her own reasons, and immunotherapy-related hyperprogression occurs later, the provider's tort liability for notification is also excluded. In addition, from the perspective of outcome-oriented loss of patient opportunity, it is difficult to support tort liability for the use of immunocheckpoint inhibitors in patients with a poor prognosis for backline or compassionate administration of immunotherapy if treatment-related hyperprogression occurs in such patients.

5.3 Legal Liability for Tumor Hyperprogression under Over-the-Counter Drug Use

Over-specification of medication refers to the use of medication in clinical medical treatment by clinicians who do not use medication in accordance with the dosage of medication, the applicable population, the indications, and the route of administration as stipulated in the instruction manual of the medication. Article 23(2) of China's Medical Practitioners Law stipulates that clinicians should follow clinical diagnosis and treatment guidelines, and comply with clinical technical operation norms and medical ethical norms, making it clear that clinicians need to carry out medical behaviors on the basis of diagnosis and treatment guidelines. However, given that diagnostic and treatment guidelines are often faced with the problem of lagging, strict adherence to diagnostic and treatment norms, including drug instructions and guidelines, may make it difficult to meet the needs of clinical diagnostic and treatment activities; at the same time, the ultimate goal of medicine is to cure diseases and save lives, and medical ethics recognizes the legitimacy of going beyond the established drug regimen to provide treatment when there are obvious deficiencies in the existing standard therapies. It can be said that the use of drugs beyond the instructions is a kind of purposeful behavior.

In comparative law, the United States, the United Kingdom, and Germany have all recognized the rationality of overdescription at the normative level[62-64]. Prior to the Physicians Law, there was no legislation on overdosage in China, but overdosage was still a common phenomenon in clinical practice. in April 2015, the Drug Risk Management Group of the Therapeutic Drug Monitoring and Research Committee of the Chinese Society of Pharmacology issued the Expert Consensus on Overdosage, which provided an initial technical level of regulation of overdosage in China. in March 2022, the Chinese Physicians Law came into force, and Article 29 of the Physicians Law stipulates that in the absence of ineffective or better treatments, overdosage should be recognized as reasonable. China's Physicians Law comes into force. Article 29 of the Physicians Law stipulates that in cases where no effective or better treatment is available, clinicians may, after obtaining the informed consent of the affected party, use treatments that are not explicitly stated in the instructions for the drug but for which there is evidence of evidence-based medicine. Article 29 of China's Medical Practitioners Law provides legal protection for Chinese clinicians to use medicines beyond the prescribed instructions, and also clarifies the preconditions for the use of medicines beyond the prescribed instructions, i.e., (1) maximizing the interests of the patient, (2) obtaining the patient's explicit informed consent, and (3) having evidence-based medical evidence.

In the specific case of oncology drug therapy, it is more common to see over-indication of drugs. The approval of oncology drug indications requires preclinical studies, phase I, phase II and phase III clinical studies, which is a long research and development cycle. During this period, many patients who are ineffective, intolerant or even have no access to standard treatments are in urgent need of more effective therapies, and the use of drugs in supra-indications brings a ray of hope for such patients. In terms of research and development, supra-indication use is also a common strategy in the development of anti-tumor drugs. Pharmaceutical companies can first promote the approval of drugs for small tumor indications, and then use the over-the-counter system to open up gaps in the use of supra-indication drugs, and then promote them to other tumor types. Therefore, in the field of oncology drug therapy, the use of drugs for over-the-counter indications is often not standardized. Taking immune checkpoint inhibitors as an example, their application certainly brings survival benefits to some patients, but not all tumors and patients can benefit from immunotherapy. For "cold tumors" with poor immune microenvironment, primary resistance to immune checkpoint inhibitors often occurs, and it is worthwhile to think twice about the selection of immune checkpoint inhibitors for this part of patients. For these patients, the choice of immune checkpoint inhibitors is worth rethinking. In clinical practice, even in the absence of appropriate indications, some clinicians often recommend immunocheckpoint inhibitors and their combination therapies for supra-indication therapy, or even advance to neoadjuvant therapy, with the ensuing risks of primary resistance, immune-related adverse reactions, and even hyperprogression. Some tumors that were originally surgically resectable have been reduced to unresectable advanced disease due to ineffective treatment leading to disease progression and loss of surgical opportunities. The piling up of immune checkpoint inhibitors for research and development and over-treatment has become a serious public health problem[65].

As mentioned earlier, there are preconditions for the use of supra-indication drugs, namely (1) maximization of the patient's benefit, (2) obtaining explicit informed consent from the patient, and (3) evidence-based medicine. First of all, the principle of maximizing the interests of patients requires clinicians to weigh the benefits of immune checkpoint inhibitors against the risks of adverse effects and hyperprogression in the best interests of patients, and to use immune checkpoint inhibitors for over-indication only when it is really necessary. If the clinician knows or should know that the patient's benefit may be low or there may be a risk of hyperprogression, the clinician's use of the immune checkpoint inhibitor beyond the indications and the resultant hyperprogression will constitute infringement. Secondly, clinicians using drugs for overindication must have evidence that the overindication will

improve the prognosis of the patient. According to the evidence grading standard of evidence-based medicine, the quality of evidence can be classified from high to low as Class A evidence: systematic evaluation and meta-analysis (Meta-analysis); Class B evidence: randomized controlled trials; Class C evidence: clinical cohort studies; Class D evidence: case-control studies; and Class E evidence: experts' opinions. Among them, expert's opinion is highly subjective and is the lowest quality evidence, which should not be used as reference evidence for supra-indications. Finally, the use of medication for supra-indications needs to be premised on obtaining the express informed consent of the affected party, and those who violate the duty of informed consent may constitute a notification-based medical tort. In terms of exclusion of liability, medical tort is also excluded if immunotherapy-related hyperprogression is caused by the patient's own reasons, such as sympathetic administration of medication, backline treatment, and adherence to immune checkpoint inhibitor therapy at the patient's own initiative or after being informed of the risks by the clinician.

5.4 Legal Liability for Failure to Monitor and Intervene in a Timely Manner in Tumor Hyperprogression

The prognosis of tumor hyperprogression associated with immune checkpoint inhibitor therapy is extremely poor, and once tumor hyperprogression occurs, the survival of the patient will be drastically shortened. After patients are fully informed of their own conditions, benefits and risks of treatment and choose immunocheckpoint inhibitor therapy, especially for patients with poor physical condition or the presence of predictive markers associated with the risk of hyperprogression, clinicians need to closely monitor the patient's condition during the administration of the drug, dynamically assess the patient's physical status and the course of the disease, and strive for early detection of immunotherapy-associated hyperprogression, and early intervention. If hyperprogression occurs, the treatment of immune checkpoint inhibitors should be stopped immediately, no other immune checkpoint inhibitors should be used, and glucocorticoids or other immunosuppressive agents should be used for symptomatic treatment, and other effective options should be replaced after the condition is stabilized to maximize the patient's prognosis. After the use of immune checkpoint inhibitors, especially for patients with a high risk of hyperprogression, clinicians who fail to detect and intervene in a timely manner with hyperprogression during the administration of the drug may constitute a medical tort of omission. If the clinician's failure to detect and intervene in a timely manner is due to the patient's own reasons, such as missed visits, liability for the related medical tort is excluded.

6. Conclusion

Immune checkpoint inhibitors have reshaped the landscape of tumor therapy, enabling tumor treatment to gradually move towards the era of "high efficiency and low toxicity" of immunotherapy, and their application has certainly brought significant survival benefits to some patients with advanced malignant tumors. Throughout the world, more and more immune checkpoint inhibitors, including improved, different targets and multi-targets, are in the R&D pipeline and undergoing clinical trials, and have been approved and marketed one after another and have come into our vision. The number of tumors for which immune checkpoint inhibitors have been approved is increasing, the level of recommendation in evidence-based medical guidelines is rising, and the number of therapeutic lines is advancing. However, under this frenzy, it should be rationally recognized that immune checkpoint inhibitors are not a panacea, and in addition to patients with primary resistance and acquired resistance that have been ineffective since the beginning of time, a smaller proportion of hyperprogressive patients with poorer prognosis are often overlooked. Immune checkpoint inhibitor-associated tumor hyperprogression is not invisible, and some patients with risk mutations and risk markers have a higher risk of hyperprogression.

When using immune checkpoint inhibitors, clinicians should comply with the appropriate laws and regulations, medical ethics and principles of diagnosis and treatment. Clinicians should pre-stratify patients according to markers and risk mutations, screen patients for possible benefits and inefficiencies according to the corresponding indicators, and fully inform patients to ensure that they make treatment choices on the basis of full knowledge of their conditions, drug risks and possible efficacy. When administering medications, clinicians should standardize the use of drugs within the scope of indications based on evidence-based medical guidelines, and monitor and intervene in a timely manner for immune-related adverse events and risk of hyperprogression. Distinction from the natural course of the tumor is a prerequisite for legal liability arising from treatment-related hyperprogression. Clinicians who violate the principles of diagnosis and treatment and blindly misuse immunotherapy, resulting in tumor hyperprogression, are legally liable, except when it is caused by the patient.

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