

Research Article

On Some Curiosities of Tumor Immunotherapy

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Abstract

This article discusses unresolved questions and contradictions in modern tumor immunotherapy, focusing specifically on the state of the immune system, checkpoint inhibitors (CPIs), chemo-immunotherapy, and the significance of systemic immune system activation. The discussion begins with the observation that, despite significant progress, the clinical success of CPI therapies remains severely limited, and the individual baseline status of the immune system is rarely taken into account in oncological immunotherapy. Drawing on the authors' own clinical experience, it is argued that robust immune system activation via PAMP-based therapy—combined with low-dose chemotherapy and reduced CPI dosages—can lead to improved tumor control while simultaneously reducing toxicity. Particular attention is paid to the role of natural killer (NK) cells, which, in the authors' view, is underestimated in current immuno-oncology. Furthermore, the article explores the interrelationships between immune status, body temperature, the tumor microenvironment, tumor mutation rates, and therapeutic efficacy. The article advocates for an individualized immuno-oncological treatment approach that systematically evaluates and specifically modulates the functional state of the immune system, thereby enhancing the effectiveness of existing immunotherapies. Such a post-treatment strategy has the potential to improve relapse prevention, long-term survival, and cure rates in cancer patients.

Keywords

Anticancer Immunotherapy, State of the Immune System, Immunostimulation, PAMP Therapy, Tumor Antigens

1. Introduction

The conviction expressed long ago by one of my colleagues—that only the immune system is capable of eliminating all tumor cells—remained largely unknown within the professional community for many years. This changed only with the emergence of checkpoint inhibitors (CPIs) and later with the introduction of chemoimmunotherapy. The progress achieved through immuno-oncological therapies involving CPIs was obvious and was recognized relatively quickly within the medical community. Nevertheless, while observing these developments, I repeatedly found myself confronted

with the same questions, some of which will be discussed below.

2. Main Contents

2.1. CPIs and the Immune System

One frequently encounters the statement that immunomodulators have fundamentally changed the treatment of tumors and that CPIs now make it possible to activate the immune system so that it can better recognize and eliminate tumor cells.

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However, how fundamental is this change if we are currently only able to make somewhat better use of the remaining functions of an already suppressed immune system? To put it very clearly: immunomodulators do not directly activate the immune system at all. We are still far from achieving a comprehensive activation of the immune system. Why this is so is a question that has repeatedly occupied my thoughts.

Another question I ask is: Why is almost nobody interested in the baseline condition of the patient's immune system before initiating immunomodulatory therapy? I would venture to suggest that this neglect is the most likely reason for the unsatisfactory results of CPI therapy. If one uses a medication intended to facilitate the immune system's fight against tumors, it would seem only logical to make an effort to understand the specific immune system with which one is dealing. However, almost no oncologists routinely assess the baseline condition of the immune system. Furthermore, it is only logical that a severely damaged immune system will respond differently to checkpoint blockade than a moderately impaired one. This fact would also partially explain why not all patients develop immune-related adverse events during or after CPI therapy and why the degree and duration of such phenomena vary across such a broad spectrum.

For many years, articles have been published describing both successes and failures in the use of CPIs. These publications document numerous efforts to identify the reasons why some patients respond to this treatment to a certain extent while others do not. Various possible factors have been analyzed and compared, including age, sex, tumor type, genetic differences, and the effectiveness of different CPI combinations. Although many interesting minor differences among these factors have been identified, none of them has been able to convincingly explain the considerable variability in patient responses to CPI therapy. To this day, the success rates of CPI therapy range between approximately 26% and 47%, while around 20% of cancer patients do not respond at all [1].

All this merely demonstrates that simply reducing inhibitory pressure on CTLA-4/6 receptors does not produce a sufficient effect when immune cells within the tumor and its microenvironment are already severely dysregulated and suppressed. In my experience, such patients require a stronger activation of the immune system. Such activation can increase the number of immune cells capable of recognizing the tumor and fighting its cells. This is because sufficiently strong stimulation of these immune cells is more effective than the inhibitory cytokines released by tumor cells.

A tumor can grow only if it has succeeded in dysregulating and effectively suppressing the immune system. It is known that tumor cells interact with immune cells in the tumor microenvironment by altering their activity and functions through cytokines for their own benefit. As a result, the immune system progressively loses control over the increasingly accelerated tumor growth. Such functional disturbances represent the principal problem in tumor treatment.

Various studies support my assumptions in this regard. CPI

efficacy in triple-negative breast cancer (TNBC) is greater in earlier disease stages than in later stages, regardless of PD-L1 expression on tumor cells, lymphocytes, and macrophages. [2] The earlier the diagnosis is established, the less the immune system has been weakened by the tumor.

2.1.1. Activation of the Immune System

TNBC is considered a difficult and therefore not always successfully treatable tumor because it mutates rapidly and frequently, causing even initially favorable responses to chemotherapy to disappear quickly. However, I believe there is a misunderstanding here. If the principal therapeutic instrument were a properly activated immune system, then the frequent mutations of TNBC cells would actually represent an advantage during treatment. This is not merely speculation, but rather something confirmed by my own experience with strong immune activation. [3] A similarly favorable response should therefore be observed in all tumors with high mutational rates.

When attempting to activate the immune system by any method, it is therefore extremely important to know its condition. Naturally, the immune response to activation attempts may be weak, adequate, or excessive. Knowledge of the baseline immune status helps determine an appropriate dose of, for example, CPIs. I have long been convinced that consideration of the potential immune response would allow improvement of CPI therapy outcomes. With a dose of immunotherapeutic agents adjusted to the condition of the immune system, it is possible not only to cause significantly fewer grade 3-4 adverse effects, but also to achieve better tumor control and longer survival. Furthermore, the fewer adverse effects occur, the more successfully treatment can be continued over a longer period of time.

After I began incorporating CPIs into my complex therapeutic approach, I soon had to progressively reduce the administered CPI doses because of adverse effects; however, this did not reduce treatment efficacy. Today, for example, I administer nivolumab at only up to 25% of the recommended dose and no more frequently than once every five to six weeks (twice the half-life). A recently published study confirmed my experience. In Sweden, physicians have greater freedom in selecting dosages for patients, whereas in many other countries the dosages approved by regulatory authorities are mandatory. One study demonstrated a significantly lower rate of grade 3-5 adverse events in patients who received reduced doses compared with traditional dosing (34% vs. 48%). After a median follow-up period of 19 months, no significant differences in survival were observed. [4] Had the condition of the immune system been assessed beforehand, the results would probably have been even better.

Today, in patients with a history of autoimmune disease, I use CPIs only in cases of a strongly suppressed immune system and only during the initial phase of therapy, for approximately two months, and at doses amounting to no more than 15-20% of the recommended levels. I assume that a similar

reduction of recommended doses should also be considered when using anti-LAG-3 agents during immune activation.

In my complex tumor therapy, the key component is PAMP therapy (Pathogen-Associated Molecular Patterns), in which very strong activation of the entire immune system is achieved through vaccinations with several attenuated live bacteria and a small amount of mistletoe extract as an enhancer. [5] This immune activation through PAMPs occurs via receptors on immune cells such as Toll-like receptors, which recognize such pathogens. These receptors then initiate a strong defensive response belonging to the evolutionarily oldest components of immune activation. Activated natural killer (NK) cells subsequently begin producing various cytokines that further increase their proliferation and activity. In addition, cytokines are produced that activate T cells.

It has been demonstrated that such activation produces a marked increase in tumor-infiltrating lymphocytes (TILs), which is regarded as a favorable prognostic sign. TILs proliferate both deep within tumors and, to an even greater extent, just beneath their surface. This fact indicates that immune cells are more likely subjected to dysregulation and suppression rather than truly exhausted because of mitochondrial insufficiency and metabolic disturbances, as is often claimed. This is further confirmed by the observation that immune cells respond quite adequately under strong activation, and even long-term repeated PAMP therapy two to three times per week does not lead to a reduction in activation. The frequency of stimulation depends on NK functional values. Laboratory monitoring confirms that the activity of NK and T-NK cells increases significantly compared with baseline values. Everything suggests that strong activation is capable of overcoming all barriers and escape mechanisms established by tumors.

This presumably also applies to T cells and may partially explain why CAR-T cells, despite initially good efficacy, often lose their effect rather quickly. It is known that NK cells not infrequently recognize excessively activated T cells as highly stressed (that is, damaged) cells and eliminate them. For me, all this indicated that when baseline NK functional test values are good, PAMP therapy should be administered somewhat less frequently and in smaller doses. Furthermore, strongly activated T cells express the protein B7H6, which stimulates NK cells to eliminate T cells in order to reduce excessive immune reactions. This is one of the protective mechanisms against autoimmune disease.

All this clearly contradicts the assumption that T cells completely lose their function because they are weakened by previous stimulation and mitochondrial impairment due to reactive oxygen species (ROS) or metabolic disturbances. Why then do they respond adequately under strong activation? I assume that not exhaustion, but rather a microenvironment saturated with various inhibitory cytokines plays the principal role in the functional loss of immune cells.

2.1.2. The Significance of Body Temperature

Furthermore, I would also like to point out the following

observation: the condition of the entire organism is reflected by body temperature, which in these cases is quite often very low. This phenomenon has long been known in chronic autoimmune conditions and cancer and is prognostically relevant because it represents a marker of significant metabolic disturbances and a severely impaired immune system. When I began paying attention to this, I was astonished by how many cancer patients live with body temperatures between 35.2 °C and 35.8 °C. Some patients were aware of this, while others were not. In earlier tumor stages, such low temperatures are observed only when an autoimmune condition existed before the tumor developed. This should be regarded as an important warning sign and considered during treatment. Under strong immune activation, body temperature normalizes relatively quickly. I have observed that even the use of MGN-3 alone for immune stimulation can gradually increase body temperature to some extent.

2.2. Adapting Immunotherapy to the Existing Immune System

Another important question is why almost all attention in immunotherapy research within oncology is focused on T cells, whereas NK cells, which represent our first and independent “line of defense” and are capable of recognizing and fighting tumor cells without assistance, remain comparatively underestimated. This issue becomes particularly important in advanced disease stages, when tumor cells increasingly lose MHC-I expression and are therefore presented to T cells less frequently. Several substances capable of effectively stimulating NK cells are known; among them, MGN-3 has been studied most extensively. Its use alone already slows tumor growth to some extent.

It is a well-known fact that checkpoint blockade in patients with mismatch repair deficiency or high microsatellite instability demonstrates response rates exceeding 90%. These are tumors that respond only briefly even to chemotherapies generally considered effective because they mutate very rapidly. However, this characteristic of such tumors actually represents a major advantage for treatment with a well-activated immune system, since newly emerging tumor antigens further stimulate immune activity. In such cases, low-dose chemotherapy must be repeatedly adjusted.

Even in the presence of known mutations, we do not possess specific antibodies for all tumors. In such cases, these antigens must be obtained, although this is not truly difficult. It has long been known that certain cytostatic agents act in such a way that they provide the immune system with substantial amounts of tumor antigens. Through the continuous supply of new antigens to the immune system, therapy becomes increasingly independent of mutations. This is the reason why the slowly emerging field of chemoimmunotherapy is effective. I utilize this effect in my complex therapeutic approach, but with significantly lower doses of administered chemotherapy in order not to suppress the activated immune system too

strongly. Years ago, it was already demonstrated that the effectiveness of CPIs in the presence of tumor antigens (in the case of neoadjuvant treatment) was greater than in their absence [6].

In recent years, the prognosis of patients with small cell lung cancer has improved significantly with the introduction of immunomodulators. Chemoimmunotherapy should work even better in such patients. Today, it would be incorrect to attempt to choose between monotherapy and chemoimmunotherapy, because the latter—particularly when reduced doses of chemotherapeutic agents are used—will always be significantly more effective. Attempts have long been made to determine where chemotherapy-free treatment approaches are possible, which in itself is a positive trend. However, chemoimmunotherapy using approximately 40-50% of the conventionally administered doses of chemotherapeutic agents, while also taking the individual condition of the immune system into account when determining CPI doses, offers far greater advantages with respect to both progression-free survival and overall survival.

My positive experience with immune activation combined with half-doses of chemotherapeutic agents confirms this. I never pursue the unrealistic goal of destroying all cancer cells with chemotherapy. Instead, the purpose of treatment is to kill or damage only part of the tumor cell population, while the remnants of these cells provide a variety of surface and intracellular tumor antigens. These antigens then encounter immune cells that are no longer suppressed and can thereby become even further activated, while the production of specific T cells is also stimulated. With this approach, low-dose chemotherapy enhances antigen exposure, as evidenced by improved antigen uptake and presentation by activated dendritic cells [7].

During PAMP therapy, all immune effector cells—and even the entire body metabolism—are activated, something that cannot be achieved through rather cautious attempts to stimulate the immune system with a single proinflammatory cytokine. The fever induced by PAMPs leads to increased blood circulation throughout the entire body and therefore inevitably within tumor tissue as well, allowing activated immune cells to reach even deeper tumor regions. In addition, the acidity within tumor tissue increases, which in turn disrupts the energy supply of tumor cells. Healthy cells receive better blood supply than tumor cells and can therefore regulate their temperature more effectively. Incidentally, strong immune activation also leads to blockade of the VEGF signaling pathway, since angiogenesis and the immune system are closely interconnected [8].

As an old joke says: there is no beneficial effect without side effects. Such a broad and powerful activation may lead to reactions to chemotherapeutic agents that are significantly stronger than usual. This can occur even despite substantially reduced doses and prolonged intervals between chemotherapy infusions, although this happens much less frequently than

CPI-related adverse effects. Therefore, the recommended laboratory monitoring during therapy remains mandatory despite the low doses administered. This strategy makes it possible to reduce dangerous adverse effects while significantly increasing the effectiveness of chemoimmunotherapy. Significant economic benefits can also be expected.

The acute as well as delayed immune-related adverse events associated with CAR-T-cell therapy could very likely be significantly reduced. Acute adverse effects in particular represent one of the main obstacles to this otherwise highly effective therapeutic approach. More than 1,000 scientific publications already address various methods for the prevention and treatment of such events. Nearly another 1,000 publications are devoted to innovative strategies and approaches in CAR-T-cell engineering. However, one possibility remains largely ignored: consideration of the baseline condition of the immune system that is intended to be specifically activated. Under such circumstances, it is hardly surprising to read statements suggesting that it remains unclear “whether interpatient variability in CAR-T-cell subsets contributes to cytokine release syndrome.” By taking the baseline state of the immune system and its possible activation into account, many tumors could potentially be overcome without significant safety concerns.

Such a combination strategy may also be supplemented and refined with established targeted precision therapies directed against specific tumor characteristics, particularly in large medical centers. Among other things, the dosages of pharmaceutical agents and local radiation therapy should be redefined in the presence of a highly activated immune system. Such an approach would significantly increase the effectiveness of tumor therapies. For example, it could become possible to achieve substantially better results in cancers of unknown primary origin (CUP syndrome), where median survival is usually less than one year.

2.3. Help the Immune System

PAMP therapy also has another highly effective field of application. Local PAMP therapy is particularly important in primary tumors that are too large for surgical intervention and in metastases growing along vessels and displaying neurotropism. In cases of recurrence, such lesions can often neither be surgically removed nor repeatedly irradiated. Directly or with the aid of imaging techniques, many of these lesions are accessible by needle. In cases where tumor lesions can be reached by needle, local administration of PAMPs makes it possible to achieve a very strong activation of immune cells directly near and within the tumor. As a consequence of the resulting strong inflammatory reaction, numerous tumor cells die, leading to the generation of specific T cells which, together with NK cells, subsequently identify and destroy additional tumor cells.

Such an approach, combined with PAMP infusions, is in the

best case capable of reducing the size of TNBC tumors by approximately half within about two months, after which these tumors may become surgically removable even in cases previously considered inoperable by surgeons.

Therefore, meaningful tumor reduction does not necessarily require prolonged standard chemotherapy with alternating toxic agents. Moreover, in such situations it is not necessary to wait for a pathological complete response before surgery becomes feasible. The three principal advantages of such an approach are: shortened overall treatment duration; substantial reduction of toxic exposure and its consequences for patients; and significant reduction in treatment costs (monthly CPI therapy costs alone amount to approximately €6,000-7,000).

Today, I know that with my complex therapeutic approach it is possible to cure a breast cancer patient with oligometastatic disease, which is generally defined somewhat inconsistently by the presence of one to five metastases. In this context, I refer only to oligometastases that cannot be surgically removed. Incidentally, it is often claimed that removing half of a cancer is no better than leaving it completely untouched. However, this is not entirely true in such generalized terms. An active immune system fundamentally changes the balance of power in the struggle between cancer and the immune system. Since we possess only a relatively limited number of immune killer cells, reducing the tumor burden is both important and beneficial. This is often the decisive factor in the body's fight against cancer, because the immune system's killer cells are then able to completely eliminate the remaining tumor cells.

When necessary, other tumors can also be successfully reduced using appropriate chemotherapeutic agents within such a treatment strategy. Exactly this effect that I have observed was documented in a recent study: operated patients in whom stage IV breast cancer was detected during mammographic screening had better survival outcomes than women who were not operated on. [9] With activating immunotherapy, survival would likely be even longer, and many more patients would achieve long-term survival.

3. Targeted Intensification of Follow-up Care

Another old yet very important question is: Why is far too little—or nothing at all—done after successful treatment to actively prevent recurrences? This long-standing and regrettable practice continues even today. The number of cancer survivors will continue to rise, increasing the number of people at risk of developing both recurrences and new types of cancer. [10] A patient undergoes surgery and/or chemotherapy with radiation therapy, but at the end of treatment, when asking what should be done next, the treating physician often says only: “Nothing. Just come regularly for follow-up examinations.” In other words, the intention is merely to detect a possible recurrence at an early stage.

Even after successfully completed therapy, a considerable number of tumor cells remain within the organism of every patient. The further course of the disease is determined by a “competition” in which it is decided which recovers first from treatment—the tumor cells or the immune system. If, at the end of treatment, the immune system remains severely impaired, the remaining tumor cells have a good chance of winning this “race.” Cancer can recur even when no metastases were detected at diagnosis and the tumors were completely removed. [11] Why, after severe toxic and psychological stress, are patients so rarely helped in this regard? It should be obvious that continuous additional support of a moderately activated immune system significantly increases the chances of survival.

Current follow-up care, however, still consists primarily of monitoring for the appearance of metastases or recurrences. A better approach would be to restore and maintain the immune system. There are already isolated attempts to administer CPIs as maintenance therapy for one year and sometimes even two years after recovery, which immediately leads to some improvement in outcomes. Yet once again, only a “crutch” is provided that offers some assistance, while the immune cells themselves—which could potentially bring the process to a true conclusion—are not activated.

Tiny groups of tumor cells that survive therapy rapidly begin to mutate in order to evade specific T cells. In addition, they intensively form a so-called “metastatic niche” to weaken the immune system locally. Patients who have overcome advanced cancer possess large numbers of tumor-specific T cells that, if maintained in a properly activated state, are capable of immediately identifying and destroying all tumor-like cells as hostile targets. To accelerate this process, CPIs may be administered in parallel. Together with activated NK cells, this could significantly increase the number of long-term survivors and cured patients.

I no longer trust an immune system that has already failed once. Therefore, after recovery, an NK functional test is initially performed every three months; only after one year are such controls performed somewhat less frequently. As long as the patient wishes, the test is then carried out approximately every six months. Should NK activity weaken, it is corrected. Various options are available for this purpose: occasional PAMP infusions, administration of Japanese MGN-3, or, in cases of only slight reduction in immune activity, for example a combination of the Chinese mushrooms ABM and *Hericium*, which among mushroom preparations most effectively stimulate NK cells.

4. Discussion

Today, I allow myself to express the hypothesis that within this complex therapy involving a well-activated immune system combined with non-aggressive chemotherapy, tissue-based characteristics and the divergences between primary tumors and metastases are of rather secondary importance. A

study showed that patients with PD-L1-negative breast cancer benefit significantly from complex neoadjuvant therapy [12].

This, of course, in no way excludes the additional use of appropriate targeted agents. Any individually suitable treatment can contribute to a curative effect during long-term therapy, even in advanced disease.

The goal should not be to oppose one treatment method against another, but rather to combine and coordinate different therapeutic elements optimally. Through a well-activated immune system, this could lead to a significant increase in the number of completely cured patients. The systematic enhancement of the body's own defense mechanisms, weakened by cancer, should today be part of every oncological treatment concept. However, this goal cannot be achieved through the use of checkpoint inhibitors alone.

Abbreviations

CPIs	Checkpoint Inhibitors
TNBC	Triple-negative Breast Cancer
TILs	Tumor-infiltrating Lymphocytes
PAMP	Pathogen-associated Molecular Patterns
NK	Natural Killer Cells
ROS	Reactive Oxygen Species

Author Contributions

Moses Schorr-Tschudnowski: Conceptualization, Methodology, Writing – original draft, Writing – review & editing

Conflicts of Interest

The author declares no conflicts of interest.

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