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Cancer Immunotherapy of Adult Solid Tumours – Some Myths, Misconceptions, Concerns and Perspectives

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The term „immunotherapy" may stir, among the general medical community and cancer patients alike, a multitude of reactions. They are as diverse as the immuno-oncological treatments themselves: from indifference to unbound enthusiasm, promising a miracle cure for cancer, from reserved scepticism to quiet pessimism. Speaking from the point of view of a medical oncologist early in his career from Romania, where national protocols and approved therapeutics are usually 2-5 years behind other European Union (EU) countries' protocols, in terms of acccess to reimbursed treatments and the latest European Medical Agency (EMA) approved therapeutics and indications, cancer immunotherapy hasn't yet made the impact it has had in the rest of the world and has barely entered the threshold of medical consciousness (at least among non-oncology specialists) and fraught with misconceptions. In an attempt to pull the vale off of immunotherapy, bringing its successes and shortcomings to light. quelling some of the concerns surrounding it (in terms of emerging treatment-related toxicities) and advocating in an unbiased tone for its place as a promising and ever-evolving cancer treatment, the following is a structured comment-and-response essay on the main topics pertaining to the state of the immunotherapy for adult solid cancers today.

Keywords: immunotherapy, immune checkpoint inhibitor, immune-related adverse reactions, PD-1, PD-L1, CTLA-4.

Immunotherapy is just a modern form of chemotherapy

False. Chemo- and immunotherapy are, by design and mechanism of action, cancer cell killers themselves, either by stopping cell growth (sometimes also inducing cell differentiation or apoptosis) or destroying the cell membrane or applying DNA damage, directly or, respectively, indirectly. Immunotherapy is different. It cannot kill cancer cells, in and of itself. It requires the host's immune system to carry out the task. It requires its T-cell lymphocyte population. Great steps for the advancement of cancer immunotherapy came with discovery of two T-cell receptors: programmed death molecule-1 (PD-1) and cytotoxic T-lymphocyte antigen-4 (CTLA-4). Two major classes of immunotherapy agents targeting the PD-1 and CTLA-4 molecules have been designed and already in use for almost 25 years, under the umbrella of immune checkpoint inhibitors (ICI): anti PD-1 monoclonal antibodies (nivolumab,

pembrolizumab, cemiplimab etc.) (eventually, its ligand present on cancer and healthy cells, PD-L1, became a target for the likes of durvalumab and atezolizumab) and anti CTLA-4 monoclonal antibodies (ipilimumab and, more recently, tremelimumab). An evocative metaphor for the effect of anti-PD-(L)1 ICIs on the immune system is „taking the foot off its break pedal", curtailing cancer's immuno-tolerance effect on the body, while „putting the foot down on a gas pedal" is more appropiate for anti CTLA-4 ICIs, rousing the immune system out of its cancer-induced slugishness. As a sidenote, these are a confirmation that neoplasms are more than just tumours; cancers are systemic diseases, treatable chronic nosological entities at that. [1, 2]

Immunotherapy is a cutting-edge anti-cancer treatment

Not necessarily. Although ICIs have been the main actors in the advancement of medical oncology in the past 20-25 years, immunotherapy has existed, in a very early state, since the 19th century (1891), in the form of the Coley toxine. It was William Coley's first attempt to „coerce" the immune system to attack cancer cells, through the use of Streptococcus pyogenes and Serratia marcescens viral strains, both active and inactive, which lead to sarcoma tumour regressions in his patients. Before the advent of ICIs, other forms of immunotherapy, like oncolytic viruses (like talimogene laherparepvec, a genetically modified herpetic virus used in advanced melanoma, applied locally), first generation anti-cancer vaccines (like sipuleucel-T, in advanced prostate cancer) and citokines (like IL-2, used in combination with bevacizumab, in advenced renal cancer) were more widely used, nowadays relegated to non-preffered or very specific indications. [3]

Since it works completely differently from chemo- and radiotherapy, immunotherapy is completely safe

Again, false. Unlike classic chemo- and radiotherapy adverse reactions (nausea, emesis, hematotoxicities, alopecia, cashexia, peripheral neuropathies, ion imbalances, palmo-plantar erithrodisesthesia, allergic-like manifestations, and radiodermatitis, post-radiotherapy pneumonia, fistulae, respectively), ICIs have a different toxicity profile, and the immune-related adverse reactions (irAEs) landscape is far-spanning in severity and diversity. It is two-faced: either extremely well-tolerated by patients, with no reported adverse reactions during treatment or in follow-up, or, with the advent of irAEs, any organ can be affected, irespective of time from start of treatment, incidents rates being proportional to the degree of organ

vascularization. Most frequently pacient- or psysician-reported irAEs are endocine in nature (hypo- or hyperthyroidism), gastrointestinal (colites, hepatites), hematological (lymphopenia), dermatological (rushes), lung-related (pneumonites), and, to a lesser degree, nephropaties and myosities. Although the body of literature cites grade 1 and 2 irAEs, according to the Common Terminology Criteria for Adverse Events (CTCAE) as being the most common, grade 5 (exitus) irAEs have been repeatedly reported, in most cases in relation to immunotherapy-induced myocardities, encephalities or hypophysities. On a more optimistic note, most grade 3 and 4 irAEs are reversible, either spontaneously, or, most often, under an immunosuppresive treatment (steroids, such as methylprednisolone or dexamethasone, or from other classes, upon steroid treatment failure – infliximab, mycophenolate mofetil, azathioprine, with or withought intravenous immunoglobulines). Interestingly, infusion reactions are a commonality in immuno- and chemotherapy, with similiar, allergic-like symptoms; usually, they are easily managed, either by cessating the perfusion, or by decreasing the drip rate, along with symptomatic treatment. [1, 2]

Upon irAEs emergence, immunotherapy doses must be adjusted, much like during chemotherapy

Untrue. There are two strategies involved with immunotherapy in clinical practice: withholding it until the sysmptoms subside to at least grade 2 or complete cessation of immunotherapy in the case of any grade 4 or recurrent or immunosupresive-resistant grade 3 irAEs. [1, 2]

Immunotherapy efficacy is profoundly influenced by temporary or permament withholding of treatment, analogous to chemo- and radiotherapy

There is evidence that there is long term benefit of immunotherapies even after treatment cessation (at least, in the case of stage IV melanoma pacients treated with nivolumab, pembrolizumab or nivolumab-ipilimumab combination), with progression-free disease at 2 to 5 years (depending on follow-up interval). Although immunotherapy's anti-cancer effect requires a longer period of time to deploy, unlike chemotherapy, its effect is more durable. [1, 2]

Immunotherapy efficacy is not dependent on its treatment start in relation to moment of surgery

Ten to twenty years ago, it was hypothesized that immunotherapy's true value could only be obtained when complete tumour resection (along with operable metastases). Going the line of chemotherapy, it was

thought that treatment efficacy is proportional to lower degrees of tumour burden. However, nivolumab, in combination with up to three cycles of platinum-doublet chemotherapy for resectable non-small cell lung cancer (NSCLC) has been recently approved, as a neoadjuvant option. In the pivotal trail, the combination treatment arm, versus the chemotherapy-alone arm, demonstrated a 37% increase in event-free survival and almost 11 times greater pathologic complet response. The rationale behind neoadjuvant immunotherapy trials is the observation that long-term immune-cell memory and tumour growth control is apparently superior when dealing with intact tumours. There are also ongoing perioperative immune trials in NSCLC, with results underway. [1, 4]

Immunotherapy efficacy is profoundly influenced by certain prior diets or medication

There is evidence that indicates to the reduced efficacy and lower overall survival of patients treated with immunotherapy and had begun an antibiotic treatment or a steroid anti inflammatory drug prior to immunotherapy initiation. In both cases, there are hypotheses in which intestinal flora disregulation, as a iatrogenic effect, and lower overall survival are linked. More than that, studies outlining the tentative link between poor immunotherapy efficay and intestinal flora disregulation also expose the positives of the reverse scenario: intestinal flora quality and diversity may be improved through probiotics or fecal translplant. In the same context, a mediterranean-type diet seems to improve overall survival in pacients undergoing immuno-oncological treatments. [1, 5]

If immunotherapy doesn't cure the pacient of cancer, then there is little hope for survival

I cannot agree with this statement. The whole point in the discovery of new therapeutical targets and advancement of new oncological therapies is to increase the benefit (in amplitude and scope) of said therapies to a wider pacient population. If by the end of the 20th century the measurement of cancer therapy efficacy was done by calculating overall response rates, disease control rates, overall survival and progression-free survival, the last two decades have shown the ever-increasing importance of patient quality of life (e.g. through the use of PROs – patient-reported outcomes). Often times, both primary and metastatic tumours would only have a partial response to immunotherapy, but without altering or even improving the patients' performance status. The high disease control rates seen with immunotherapy, which increases the number of „long survivors" of melanoma, renal and lung cancer and cancers of the head and neck, to name a few (even in very poor-prognostic patient populations, e.g. brain metastases), is

also non-negligable. The major disadvantage of immunotherapies over chemotherapy is the time-to-response time: it has been reported that the minumum would be 2-3 months, as opposed to a median value of 2-4 weeks, in the case of most chemotherapy regimens; even more spectacular, some forms of targeted therapies (e.g. BRAF and MEK inhibitors for BRAF-positive melanoma) have an average time-to-response of a couple of days, even a few hours. [1, 2]

All cancer patients, no matter their performance status, disease stage or primary tumour location, will benefit from immunotherapy

Sadly, that is not the case. Firstly, most data we have on immunotherapy benefit is on stage III or IV disease; there is a distinct lack of information in stages I and II at the moment, but ongoing clinical trials will hopefully give important insights. Secondly, even when immunotherapy comes with a high recommendation as a treatment option, some patiens will derive little to no benefit. For instance, in the case of nivolumab for second-line treatment of NSCLSC after chemotherapy-failure, there are situations where the PD-1 inhibitor increases the chance of patient death within 3 months of initiation – there are certain negative predictors of immunotherapy response to take into account, such as: progressive disease as best response to prior chemotherapy, serum C reactive protein to serum albumin ratio greater than 0,3, neutrophile to lymphocyte ratio greater than or equal to 5, Eastern Cooperative Oncology Group (ECOG) performance status greater than or equal to 2, and last but not least, the increasing in number of metastatic sites (more than 1). In very carefully selected patient populations, initiation of palleative chemotherapy could be an option, if the risk-benefit scale is tilted towards a high chance of disease-related symptom control. [6, 7]

Immunotherapy has no effect on central nervous system (CNS) tumours, which can only be treated through surgery, radiotherapy or other systemic therapies

False. Immunotherapies (ICIs, to be more specific) have a great advantage over other systemic cancer treatments: they themselves don’t need to traverse the blood-brain-barrier - being engineered immunoglobulines at heart, one would expect low levels of intra-cerebral spinal fluid (CSF) concentrations - instead, it’s the activated T-cells that find a way into the CSF and attack the cancer cells. In the absence of absolute contraindications, the dual ICI combination of nivolumab and ipilimumab is

the gold standard treatment option for stage IV melanoma or renal cancer with asymptomatic brain metastases. [1, 2]

Immunotherapy cannot be safely administered to patients with pre-existing autoimmune diseases and lack any benefit in this patient population

Pre-existing autoimmune diseases represent a relative contratindication for immunotherapy initiation. Neither lower efficacy, nor increasing toxicities have been shown to affect this patient population to a statiscally significant degree. A multidisciplinary team, including a rheumatologist and/or immunologist, is the key to best decision making. [1, 2]

Immunotherapy is not safe for pregnant women or who are breastfeeding

Since breastfeeding or pregnant women are almost always excluded from immunotherapy trials, there is little knowledge of the effect of ICIs to the mother and fetus; therefore immunotherapy is not recommended in this patient population. Moreover, adequate contraception must be followed during immunotherapy treatment and in follow-up, for at least 5 months for female patients, and 8 months, respectively, for male patients, after the last dose. [1, 2]

Immunotherapy is not safe for patients undergoing vaccination

Unfortunetely, there is little evidence in this regard. Vaccination should only be considered after careful analysis of risks and benefits. Still, there are certain recommendations outside of currently available immunotherapeutics monographs: 1) in general, analogous to pivotal study protocols, any vaccines 30 days prior to treatment start and up to 100 days after last ICI dose are disallowed; 2) any vaccine with active or partially active viral agents (chickenpox, anti-herpes, yellow fever, rotavirus etc.) are disallowed; 3) anti-flu vaccines with inactived viral agent are allowed (ongoing studies are evaluating its safety). [1, 2]

Immunotherapy may lead to dormant or undiagnosed infection reactivation

There is a growing body of evidence of infectious diseases (mostly patients with concomitent AIDS or pulmonary tuberculosis) which become alarmingly active again during ICI treatment. The first recorded case from Romania has been recently reported, of a male patient with NSCLC who, under nivolumab treatment, experienced pleural and acute pericardial tuberculosis, having been diagnosed and treated for pulmonary tuberculosis years before. Apparently, there are two mechanistic theories, possibly intertwined, that may explain this phenomena: hypersensitive response similar to immune reconstitution inflammatory syndrome or immune checkpoint–related lymphopenia. [1, 8]

Immunotherapy has revolutionized cancer treatment, especially in terms of overall survival and increasing the number of „long survivors"

I am in agreement with the above statement. As an example, a recent American populational study (underlining real-world data) has shown an increase in 3-year overall survival from 6% to 18% in patients with stage IV NSCLC, during 2013 to 2018, after the implementation of ICIs in clinical practice. [1, 9]

Immunotherapy is one of the most highly studied areas in the oncology treatment landscape

I would say that is accurate. Relevant in this regard is awarding the Nobel prize for physiology or medicine in 2018 to two eminences in immuno-oncology: Prof. Dr. Tasuku Honjo and Prof. Dr. James Allison, discoverers of the PD-1 molecule and CTLA-4 molecule, respectively. Many novel therapeutic targets have been discovered and new therapeutics have been developed and approved by regulatory bodies since then (e.g. relatlimab, an anti-LAG-3 monoclonal antibody, is FDA-approved, in combination with nivolumab, for the treatment of stage IV melanoma). [1.3]

Conclusions

While there is still a long road ahead in eradicating adult solid tumours as a nosological entity, there is no doubt in my mind that immunotherapies (especially ICIs) are a valid treatment option and a monumental milestone in antineoplastic therapeutical research, not ommiting further inquiries in better dosing schedules [10] or better irAEs diagnosis and management. There might come a day when the only remaining systemic treatment in the medical oncologist's armamentarium would be immunotherapy, given in early stage disease or perhaps even as prophylaxis in high-risk patients with certain genetic

features. It could be 50, 100, 200 years from now, but considering the many strides this ”Wunderkind” in systemic oncological treatments has made in the last 15 years, I remain cautiously optimistic regading its future applications and impact it will have: the spearpoint aiming at the Holy Grail of medical oncology – a definitive and safe cure for cancer.

References

1. Butterfield L.H., Kaufman H. L, Marincola F.M. Cancer Immunotherapy: Principles and Practice. 2nd edition. Demos Medical Publishing, 2022

2. Devita V.T. Jr., Lawrence T.S., Rosenburg S.A. Cancer: Principles and practice of oncology, 12th edition. Wolters Kluwer. Cap 17-20: 202-241. 2023

3. Zhang Y., Zhang Z. Cellular & Molecular Immunology (2020) 17:807–821

4. N Engl J Med 2022;386:1973-85

5. Soldati et al. J Transl Med (2018) 16:75

6. Inoue T., Clin Lung Cancer. 2018; 19(2):e171-e176

7. Barlett E et al. Cancer 2019; DOI: 10.1002/cncr.32506

8. Pirvu E., Cocioaba C. Journal of Medical and Radiation Oncology, Volume II, Issue 2 (December 2022) 59-65

9. Cancers 2021, 13, 4846.

10. Mitchell A.P., Goldstein D.A. Cost Savings and Increased Access With Ultra-Low-Dose Immunotherapy. JCO. Volume 41, Issue 2: 170-172.