

What do we know about cancer immunotherapy? Long-term survival and immune-related adverse events.

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Abstract

Immunotherapy delivered a new therapeutic option to oncologist: Ipilimumab (anti-CTLA-4), Nivolumab and Pembrolizumab (anti-PD1) and Atezolizumab (anti-PD-L1) increase overall survival and show a better safety profile compared to chemotherapy in patients with metastatic melanoma, lung, and renal cancer among others. But all that glitters is not gold and there is an increasing number of reports of adverse effect while using Immune-checkpoint inhibitors. While chemotherapy could weaken the immune system, this novel immunotherapy could hiper-activate it, resulting in a unique and distinct spectrum of adverse events, called Immunes-related adverse events irAEs. irAEs ranging from mild to potentially life-threatening events can involve many systems, and their management is radically different from that of cytotoxic drugs: immunosuppressive treatments, such as corticoids, infliximab or mycophenolate mofetil usually results in complete reversibility, but failing to do so can lead to severe toxicity or even death. Patient selection is an indirect way to reduce adverse events minimizing the number of subjects exposed to these drugs: unfortunately PDL-1, the actual predictive biomarker wouldn't allow clinicians select or exclude patients for treatment with checkpoint inhibitors.

Keywords: Immunotherapy, Adverse events, Management, Response rates.

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Introduction

Immunotherapy is a new therapeutic option in Oncology. The recent introduction of Immune Checkpoint Inhibitors (ICI) has led to a paradigm shift in many cancers such as melanoma, lung or renal cancer among others. They are monoclonal antibodies against the checkpoint molecules CTLA 4, PD-1 and PD-L1 antigens.

CTLA-4, a homolog of CD28, bound with higher affinity to B7-1 and B7-2 and inhibited CD4 T-cell activation; so anti-CTLA-4 (Ipilimumab) promoted CD4 T-cell activation against the tumor.

PD-1 expression on T-cells, which can interact with PD-L1 expressed on cancer cells, inhibiting T-cell activation and perhaps inducing a state of anergy in immune cells present in the tumor. Blocking the PD-1/PD-L1 pathway with Nivolumab/Pembrolizumab (anti-PD1) or Atezolizumab (anti PDL1) can revert this condition, promoting cancer cell elimination by activated T-cells.

Others specific immunotherapies such as vaccines, T-cell engager or oncolytic virus are under investigation. Checkpoints inhibitors have shown a significant improvement in overall survival in metastatic diseases, even after discontinuation of treatment, a high percentage of patients maintained a prolonged tumor response. Nevertheless, the immune response leads to different adverse effects from those produced by traditional chemotherapy or targeted therapies; chemotherapy produces adverse events related to a weakened immune system while immuno-checkpoint generate an over stimulated immune system leading to "auto-immune like adverse events" irAEs.

They may appear at the beginning, during, or after the end of treatment.

The most frequent manifestations are dermatological, digestive and endocrine, but renal, pulmonary and nervous system related disorders may also occur, among others. The onset of the toxicity is in first 16 weeks in 85% of the cases [1].

They range from mild and reversible to life-threatening and early recognition seems to be the key to avoid adverse fatal events. Approximately 58-85% of toxicity is reversible after steroid treatment if started promptly [2].

Reversible irAEs included fatigue, pruritus, rash, myalgia, arthralgia, loss or change of appetite and hypo-hyperthyroidism. Otherwise irreversible adverse events consisting of diabetes mellitus, uveitis, arthritis and some case of hypothyroidism [3]. Severe irAEs that potentially can be life-threatening are hepatitis, colitis, hypophysitis, pneumonitis, myocarditis, Guillain-Barré, myasthenia gravis and encephalitis. For proper management it is very important to detect them early and start the appropriate treatment as soon as possible; so deep knowledge of irAEs is a priority for oncologist of the new era.

The efficacy of immunotherapy

Treatment with immunotherapy seems to be effective for different tumor histologies and independent of driver mutations. Survival benefit and response rate is different depending on the drug used, but adverse events are very similar.

Ipilimumab

Ipilimumab is a fully human monoclonal IgG1 anti-CTLA-4 antibody. It was the first to be approved by the FDA and EMA. In 2011, as second-line for metastatic melanoma, and two years later, in 2013, as first-line for the same situation after showing benefit in survival rate [4].

In 2015, Schandendorf D published results of an analysis of pooled OS data from several clinical trial phase II and III. Ipilimumab improves OS until 11.4 months (95% CI, 10.7-12.1 months) with a 3-years survival rate of 22% (95% CI, 20-24%) [5]. In addition, as of the third year of treatment, a plateau appears and extends up to 10 years in some patients.

The most recent research evaluates the role of ipilimumab in the adjuvant setting for melanoma stage III. In a phase III study, it's compared to placebo after adequate surgery. Patients received ipilimumab or placebo and the median recurrence-free survival was 26.1 months vs. 17.1 months respectively, with a 3 year recurrence-free survival of 46.5% vs. 34.8% [6]. Data of OS is not available yet.

Nivolumab

Nivolumab is a human monoclonal IgG4 anti-PD-1 antibody. In 2014 it obtained its first approval for unresectable or metastatic melanoma after ipilimumab or a BRAF inhibitor. Previously, the results of CheckMate-037 had demonstrated that ORR was 31.7% (95% CI, 23, 5-40,8) for nivolumab vs. 10.6% (95% CI, 3.5-23.1) in the chemotherapy group, after ipilimumab [7].

In 2015, approval of nivolumab was extended to other indications such as squamous and non-squamous NSCLC after progression on platinum chemotherapy, metastatic RCC after progression on antiangiogenic therapy and, later Checkmate-066 showed an HR 0.42 in favor of nivolumab against dacarbazine and a 1-year OS rate of 72.9% vs. 42.1% respectively with ORR 40% with nivolumab vs. 13.9% with dacarbazine, Nivolumab was also approved as first line therapy of metastatic melanoma.

Recently, in February 2017, Nivolumab has been approved by Food and Drug Administration for bladder cancer platinum-pretreated patients.

Pembrolizumab

Pembrolizumab is a fully humanized monoclonal IgG4 anti-PD-1 antibody. In 2014, Pembrolizumab was approved by FDA for unresectable or metastatic melanoma after Ipilimumab, but in 2015 the phase III trial Keynote-006 evidenced a significant improvement in OS in favor of Pembrolizumab [8]. So Pembrolizumab was approved for first line therapy of metastatic melanoma. The same year, it was obtained the approval for PD-L1+, advanced NSCLC previously treated based on the results of the KEYNOTE-010 study. March 2017, phase III trial KEYNOTE-045 demonstrated a significant benefit in survival in patients treated with pembrolizumab compared with the standard second-line chemotherapy.

Atezolizumab

Atezolizumab is a fully humanized monoclonal IgG1 anti-PD-L1. To date, has only been approved by the FDA as the second line for advanced NSCLC and locally advanced or metastatic urothelial carcinoma. Approval for NSCLC was based on results of OAK and POPLAR trial, where it's was demonstrated a clear improvement in overall survival versus chemotherapy. It's was approved in 2016, for urothelial cancer pretreated with platinum based on IM vigor 210 phase II trial.

Benefit of combination immunotherapy

The most recent studies investigate the combined use of immunotherapy with other immunotherapy drugs or chemotherapy, target therapy, and radiotherapy. The hypothesis is that the combined treatment has a synergistic or additive effect. The main problem is the increase in serious adverse effects.

The phase III CheckMate 067 compared ipilimumab alone vs. nivolumab alone vs. nivolumab and ipilimumab in combination for untreated patients with unresectable or metastatic melanoma [3]. The results showed a significant improvement in favor of combination: PFS 11.5 months with combination vs. 6.9 months with Nivolumab vs. 2.9 months with ipilimumab, HR 0.42 (99.5% CI 0,31-0,57) and ORR was 57.6% vs. 43.7% and 19% respectively.

On the other hand, a phase II KEYNOTE-021 evaluated the effect of adding pembrolizumab to carboplatin and pemetrexed for metastatic non-squamous lung cancer. The combination obtained an ORR of 55% vs. 29% for chemotherapy alone [8].

More studies are necessary to understand the efficacy and safety of different possible combinations of treatment.

Persistent responses

It seems surprising that patients who discontinued treatment with immunotherapy for other reasons than tumors progression, primarily toxicity, continued to respond (complete or partial response) in up to 70% of cases [3]. Currently, the question is how long should we treat patients with immunotherapy? More studies are necessary to answer this question.

Immune toxicity spectrum of checkpoint blockade agents

Dermatological

The dermatological manifestations are the most common and those that appear earlier, approximately 2-3 weeks after the beginning of the treatment. It is common to see them after the first dose [1]. The most frequent are pruritus, maculopapular rash, erythema, alopecia, hypertrichosis, lichenoid keratosis, and vitiligo. Other rarer and potentially fatal are the Stevens-Johnson syndrome and toxic epidermal necrosis. They are more common with CTLA 4 inhibitors, however oral mucositis and vitiligo are more prevalent with anti-PD1/anti-PD-L1

therapy [9]. Approximately, 47-68% patient on anti CTLA-4 therapy and 30-40% with anti-PD-1/anti-PD-L1 therapy. For diagnosis, the tools we can use depend on the severity: mucocutaneous examination, serum tryptase and IgE levels and skin biopsy depend on the grade of severity.

Gastrointestinal

This type of events usually appears 5-10 weeks after the second dose. Among the digestive manifestations are diarrhea, colitis, nausea, vomiting, gastritis, pancreatitis, celiac disease [1]. The anti-CTLA4, especially Ipilimumab is the one that has been mostly related to diarrhea and colitis (30-40%) [4]. However, it has been seen that patients subsequently treated with anti-PD-1/anti-PD-L1 antibodies do not develop diarrhea or colitis [10].

To identify this is prior to doing the differential diagnosis with stool microscopic examination for ova, parasites, stool culture and antigen for c. Difficile evaluate progression of primary disease and endoscopy.

Liver

Disorders of the liver appear 12-16 weeks after starting treatment with Ipilimumab. It is often seen after administration of the third dose [1]. Unexplained transaminases elevation is a common signs of Hepatitis; it can be asymptomatic or accompanied by fatigue and fever. It appears in 10% of patients treated with anti-CTLA 4 and about 20% of patients treated with the combination of anti-CTLA 4 and anti PD1/PD-L1 [1]. Differential diagnoses should include many causes of

liver disease such as viral hepatitis, liver metastases, hepatotoxic drug: Anamnesis, physical exploration, hepatotropic virus serologies, CT or liver biopsy should be performed in order to rule out secondary causes of hepatitis.

Endocrine

Usually, these effects appear 9 weeks after initiation of treatment with Ipilimumab [1]. The alterations that may appear are hyper/hypothyroidism, hypophysitis, adrenal insufficiency, and diabetes. Hypothyroidism is more prevalent with anti-CTLA 4 while hyperthyroidism and hypophysitis are more prevalent with anti-PD-1 and anti-PDL1 antibodies [1].

It is difficult to diagnose these entities due to its non-specific symptoms: fatigue, anorexia, nausea, headaches. The diagnosis is mainly made with hormonal determinations: TSH, ACTH, LH, FSH, prolactin, GH, testosterone.

Lung

The manifestations that may appear are pneumonitis, pleuritis, sarcoid-like granulomatosis. Pneumonitis is the most frequent and appears in 1% of patients treated with anti-CTLA 4 and approximately 5-7% of grade 3 or higher in patients with NSCLC treated with Nivolumab and Pembrolizumab [11].

It should be ruled out in all patients who begin with progressive shortness of breath, dry cough, and fever. The suggested tests are CT and bronchoscopy to rule out an infectious cause (Table 1).

Table 1. Other manifestations.

Eyes	Uveitis, conjunctivitis, blepharitis, retinitis, choroiditis, orbital myositis and episcleritis scleritis.
Renal	Acute kidney injury, granulomatous interstitial nephritis, lupus-like glomerulonephritis.
CNS	Posterior reversible encephalopathy syndrome, Guillain-Barre syndrome, myasthenia gravis, transverse myelitis and peripheral neuropathy, aseptic meningitis, meningo-radiculo-neuritis.
Hematologic	Hemolytic anemia, thrombocytopenia, neutropenia, pancytopenia, hemophilia.
Muscle	Myopathies, arthritis.
Cardiovascular	Myocarditis, pericarditis, vasculitis.

Management of irAEs

In the last year's immunotherapy has demonstrated his useful in many types of tumors and the number of patients receiving this kind of treatment it's increasing; although these new immunotherapies also generate dysimmune toxicities by unbalancing the immune system, favoring the development of autoimmune manifestations [12].

In this setting, many guidelines are been developed and all they are agree with the use of corticosteroids and immune-modulating agents. But the management of irAEs is more complex, the Gustave Rousy cancer center published a guideline that comprises five pillars: these are prevented, anticipate, detect, treat and monitor the irAEs [9].

In preventing it's important to know the immune toxicity spectrum as we describe previously and identify dysimmunity risk factors as personal and family history of autoimmune disease. It is important to identify the presence of opportunistic infections (tuberculosis infection, pneumocystis pneumonia, chronic hepatitis among others) because the administration of immune checkpoint blockade (ICB) could be responsible for inflammatory reactions against such pathogens by refreshing the anti-pathogen immune response [9].

For anticipate the Gustave Rousy develop an immunotherapy baseline checklist that could be useful to identify the occurring of new abnormalities or toxicity [9]. When a new abnormality its detected it's important to rule out that it's secondary to a disease progression or a fortuitous event before defined as a treatment-related dysimmune toxicity. For example in a meta-

analysis about safety and efficacy of Nivolumab the risk of irAEs grade ≥ 3 it's only 0.12 and the most common grade ≥ 3 were hypophosphatemia (2.3%) and lymphopenia [13].

Currently, management guidelines are based on empirically directed immune-modulating agents (corticotherapy and immunosuppressive drugs) and on the knowledge of autoimmune diseases [14]. Before the initiation of corticosteroids or other immunosuppressive drugs, it is necessary to rule out any associated infection.

Corticosteroids should be employed at initial doses used to treat autoimmune diseases (1 mg/kg/day or more), the duration it is generally of 2-4 weeks and 58-85% of toxicity is reversible with steroid treatment [2], after corticosteroids must

be reduced gradually over a period of at least 1 month to avoid that the IRAE recur [12].

When the irAEs are steroid-refractory, immunomodulatory or immunosuppressive agents such as tumor necrosis factor (TNF)-alpha antagonists, azathioprine and mycophenolate mofetil (MMF) may be effective [15]. While the anti-TNF-alpha has an immediate therapeutic effect, the other immunosuppressive drugs such as azathioprine and MMF only become effective after several weeks [16].

Another key point it's if the management should be ambulatory or inpatient care, guidelines suggest that grade ≥ 3 should be treated inpatient (Table 2).

Table 2. Management of irAEs [12].

Severity CTCAE grade	Ambulatory vs. inpatient care	Corticosteroids	Other immunosuppressive drugs	Immunotherapy
1	Ambulatory	Not recommended	Not recommended	Continue
2	Ambulatory	Topical steroids or systemic steroids oral 0.5-1 mg/kg/day	Not recommended	Suspend temporarily(a)
3	Hospitalization	Systemic steroids oral or IV 1-2 mg/kg/day for 3 days then reduce to 1 mg/kg/day	To be considered for patients with unresolved symptoms after 3-5 days of steroid course. Organ Specialist referral advised	Suspend and discuss resumption based on risk/benefit ratio with the patient
4	Hospitalization intensive care unit consider	Systemic steroids methylprednisolone 1-2 mg/kg/day for 3 days then reduce to 1 mg/kg/day	IV To be considered for patients with unresolved symptoms after 3-5 days of steroid course. Organ specialist referral advised	Discontinue permanently

(a) Outside skin or endocrine disorders where immunotherapy can be maintained.

And finally, monitor evolution, the time needed for irAEs resolution can highly vary across the various types of toxicities. For example, the median time to resolution of irAEs of any grade secondary to nivolumab ranged from 3.3 weeks for hepatic AEs to 28.6 weeks for the skin [2]. In addition to being aware of the risk of relapse or recurrence of irAEs or for immunosuppression complications [9].

Relation between irAEs and response rates

The presence of adverse effects related to treatment with some anti-tumor drugs as for example anti-EGFR has been associated with a higher rate of response, in the case of irAEs to immunotherapy, their relationship between their presence and the response rate is not completely clear. In a reviewed retrospectively of patients with melanoma treated ipilimumab, no difference in OS or TTF was detected when patients were stratified by the presence or absence of irAEs of any grade [17].

In another retrospective analysis of patients with melanoma treated with nivolumab, in a multivariable analysis adjusting for differences in number of nivolumab doses received, baseline LDH and tumor PD-L1 expression ORR was significantly better in patients who experienced irAEs of any grade compared with those who did not, with greater benefit in patients who reported three or more IRAES [2].

With current evidence cannot be concluded if the presence of irAEs is related to the rate of response, PFS or OS.

Impact of use of immune-modulating agents (IMs)

The use of immune-modulating agents (corticosteroids and immunosuppressive drugs as anti-TNF-alpha or mycophenolate) due to their immunosuppressive effect might be related to a decreased effectiveness of immunotherapy, however several studies show no significant difference in the ORRs between patients who received this kind of treatment versus who did not receive IMs.

For example, in a retrospective analysis that includes two phase III trials with patients who received nivolumab 3 mg/kg/2weeks for melanoma, the ORR was 29.8 in the group of patients that received IMs and 31.8 in the group of patients that nor received IMs [2].

In another retrospectively reviewed of patients with melanoma treated with Ipilimumab, there was no difference in OS or TTF when patients were stratified by the administration of systemic corticosteroids to treat an irAEs [17].

Conclusion

Immunotherapy is a promising approach for the treatment of cancer, probably changing the paradigm of this illness. The independence from tumor histologies and/or driver mutation could reduce the necessity of repeated biopsy, improving the quality of life and lowering the rate of adverse effect.

Sustained response even when patients discontinue treatment will obligate oncologist to create the term "Treatment-free survival" to indicate patients without cancer progression and without active treatment.

However, all that glitters is not gold and immunotherapy-treated patients could experiment life-threatening adverse effect especially when physicians don't follow the five pillars of immunotherapy published by Gustave Rousy cancer center; prevent possible adverse effect and strict monitoring our patients is essential to avoid the potentially harmful effect of Immune-checkpoints inhibitors.

Another big issue is patient selection, nowadays PDL-1 is far from the "perfect" predictive biomarker. As stated previously PDL-1/PD-1 inhibitors release the brake to allow T-cells to fight cancer by inhibiting immune system checkpoints. This strategy allows us to fight cancer when the battlefield is downhill or when the tumor is "immunogenic" (hot) while is clearly. Useless when cancer is low immunogenic (cold tumor). Immune-checkpoints inhibitors need an activated immune system to work: next challenge is to find a clinical marker capable of differentiating a "hot" or a "cold" immune system allowing the physician to decide which patients could benefit from this molecules.

Oncologists are at the beginning of a new age of cancer treatment: we are few steps away from changing the paradigm of cancer treatments allowing patients to have a treatment with pleiotropic, long lasting and less toxic effect using our immune system to fight The Emperor of All Maladies.

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