Harnessing the immune system to provide long-term survival in patients with melanoma and other solid tumors

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Accumulating data from patients treated with checkpoint inhibitors and other immunomodulatory agents indicate that harnessing the power of the immune system is integral to achieve improve long-term cancer containment rates and prolong patient survival. Due to their mechanism of action, immunotherapeutic approaches have the potential to be effective against almost every tumor type. Durable responses to immunotherapy and prolonged patient survival have indeed been documented in individuals with melanoma, as well as kidney and lung cancer. These advances call for the re-evaluation of how clinical benefit is measured in an era in which long-term tumor control and survival are achievable treatment goals.

Introduction

Recently, there has been a surge of interest in moving the focus of cancer research away from the cancer cell and toward the host and microenvironment in which tumors grow.[1] Unlike conventional chemotherapies and targeted anticancer agents, which act directly on malignant cells or proximal stromal cells, immunotherapies have an indirect mechanism of action. They potentiate or reactivate ongoing, inefficient antitumor immune responses and break tumor tolerance, which is one of the major strategies used by neoplastic cells to escape immune recognition.[2,3] Positive results from clinical trials with regimens that activate the immune system, or tackle immunosuppression, have led many to believe that immunotherapy is now the fourth cornerstone of anticancer treatment.[4,5] As oncoimmunology enters this exciting new era, we discuss how immunotherapy commonly results in long-term tumor suppression, and highlight the clinical relevance of this outcome to patients with advanced disease.

The Importance of Durable Tumor Control

Experience with immunotherapy has shown that cancers can be contained in such a way that patients may live for a prolonged period of time, with reduced or no symptoms, and with a quality of life that allows them to continue to work and/or spend valuable time with their family.[6] This substantial increase in life expectancy is an important outcome for patients with advanced solid tumors, especially when the chances of complete and permanent disease eradication are so small.

The Role of Immune-Directed Cancer Therapy in Cancer Containment

Our rapidly growing understanding of antitumor immunity and how it can be avoided has led to new immunotherapeutic regimens that promise to be more successful than previous anticancer therapies. Although immunotherapy has the potential to be effective in patients affected by all tumor types, to date, its promise has primarily come to fruition with therapeutic advances in melanoma.

Interferon

In 1995, interferon-α2b (IFN-α2b) became the first immunotherapeutic agent approved by the US Food and Drug Administration (FDA) for the adjuvant treatment of Stage IIB/III melanoma. Additional trials with IFN-α2b demonstrated that efficacy not only was marginal for the overall patient population, but also was unaffected by dose or treatment duration.[7,8] Strong evidence is now emerging that IFN-α2b is only beneficial in patients with an ulcerated primary tumor, irrespective of the presence of lymph node metastases, suggesting that ulcerated melanoma is a relatively distinct biological entity.[8-14] Moreover, disease stage is also an important consideration. The effect of IFN-α2b is highly significant in patients with Stage IIB and sentinel node (SN)-positive Stage III melanoma, but blunted in palpable node-positive patients.[12] Adjuvant IFN-α2b has been shown to consistently reduce the risk of disease recurrence, distant metastases, and death by 35–44% among patients with SN-positive disease and an ulcerated primary tumor. Importantly, these benefits are preserved

with long-term follow up, indicating that the patients who respond to adjuvant IFN-α2b within this subgroup can have long-term survival.[15] A prospective, randomized, Phase III clinical trial (EORTC 18081) is currently evaluating the effects of adjuvant pegylated-IFN-α2b on recurrence-free survival and overall survival (OS) in patients with thick, ulcerated primary melanomas.[16]

Interleukin-2

Interleukin-2 (IL-2), the second exogenous cytokine for which antitumor activity against solid tumors was demonstrated, was approved by the FDA in 1998 for the treatment of metastatic melanoma. A minority of patients (~6%) treated with high-dose IL-2 manifest complete tumor responses lasting for 5 to > 10 y.[17] Nonetheless, high-dose IL-2 can cause serious side effects, and is generally reserved to patients who are otherwise healthy. High-dose IL-2 is also an important component of adoptive T-cell transfer protocols.[18] However, current evidence indicates that the high rates of durable responses observed in this setting may not be dependent on IL-2.[19] These approaches are complex and remain investigational at present.[20]

Overcoming Immunosuppression is the Key

Overcoming immunosuppression appears to be a much more powerful intervention than short-lived immunostimulatory strategies, and the current concept of "inhibiting the inhibitor" to release the breaks on the immune system appears to be a particularly potent approach.[6] In 2011, ipilimumab, a monoclonal antibody specific for cytotoxic T lymphocyte-associated protein 4 (CTLA4), which transmits an inhibitory signal to T cells, became the first agent in the history of melanoma to be approved by FDA based on a demonstrated survival benefit in patients with advanced disease.[12] In a Phase III clinical trial (MDX010–20), the efficacy of ipilimumab alone or in combination with a gp100-derived peptide vaccine (gp100) was compared with that of gp100 alone in patients with advanced melanoma who had received prior therapy.[21] Patients were monitored for up to 55 mo. Those treated with 3 mg/kg ipilimumab, with or without gp100, had a significantly improved survival outcome as compared with patients who received gp100 alone. The median survival in ipilimumab plus gp100 and ipilimumab alone groups was 10 mo and 10.1 mo, respectively, as compared with 6.4 mo for patients treated with gp100 alone. This corresponded to a significant reduction in the risk of death of 32% and 34%, with hazard ratios (HR) = 0.68 and 0.66, respectively. OS rates in the ipilimumab plus gp100 group, ipilimumab alone group, and the gp100 alone group were 43.6%, 45.6%, and 25.3% at 1 y, and 21.6%, 23.5%, and 13.7% at 2 y, respectively.[21] The effect of ipilimumab on OS was independent of age, sex, baseline serum lactate dehydrogenase levels, stage of metastatic disease, and previous IL-2 therapy.[21]

In this Phase III clinical trial, reported by Hodi et al., 38 (7%) ipilimumab-treated patients achieved complete or partial tumor responses as their best on-study response. Although limited in number, responses were durable, lasting more than 4 y in some cases.[21] Additional 82 patients had stable disease (SD), totaling a disease control rate (DCR) of 22%.[21] Interestingly, and perhaps characteristic of immunotherapy, some patients had an improvement in best response after the completion of induction therapy. In the ipilimumab plus gp100 group, 3 patients with progressive disease improved to SD, 3 with SD gained a partial response (PR), and 1 with a PR improved to a complete response (CR). Along similar lines, in the ipilimumab alone group, 2 patients with SD improved to a PR and 3 with a PR improved to a CR.[21] Importantly, durable disease control and prolonged survival were achieved in the absence of continued ipilimumab treatment. Retreatment (4 intravenous administrations of 3 mg/kg ipilimumab at 3-wk intervals) was offered to patients who progressed upon responding to the first induction treatment, leading to an objective response rate (ORR) of almost 20%, and more than 65% of patients re-attained disease control.[22]

The observation that SD in response to immunotherapeutic agents such as ipilimumab is a common outcome is important. With conventional chemotherapy and targeted anticancer agents, SD is usually transient and not indicative of a meaningful clinical effect. Conversely, disease stabilization in response to immunotherapy is often durable. As a result, patients with SD have similar survival outcomes to patients with an objective response.[23] This, together with the observed evolution of responses over time, may simply reflect the mechanism of action of immunotherapy.

The positive impact of ipilimumab on survival has been consistently observed across all lines of therapy, treatment regimens and dose levels.[24-27] Furthermore, accumulating data suggest that ipilimumab can induce long-term survival even in patients expected to have a particularly poor prognosis.[28,29] In a landmark analysis of 177 patients treated with ipilimumab in Phase II clinical trials at the National Cancer Institute, 13–25% of patients survived at least 5 y, and for the most part, survival curves plateaued for patients surviving beyond 4 y.[30] In a second study of extended treatment or follow-up in patients previously enrolled in 1 of 4 different Phase II clinical trials, the 5-y survival rate for patients treated with 3 mg/kg ipilimumab was approximately 17% and ranged from 18% to > 49% among patients treated with a dose of 10 mg/kg. Importantly, a meaningful proportion of patients continued to survive beyond 5 y.[24] Recently, pooled data from 4846 patients who received ipilimumab within a clinical study or expanded access program was analyzed to provide a more precise estimation of long-term survival achieved with ipilimumab in patients with advanced melanoma. The median OS was 9.5 mo (95% confidence interval: 9.0–10.0). Even more striking was the plateau in survival, which began approximately 3 y after treatment initiation for 21% of patients and continued for up to 10 y. The durability of long-term survival did not appear to be impacted by prior therapy, dose or treatment regimen.[27] Further investigation of the optimal ipilimumab dose (3 or 10 mg/kg) and administration protocol to achieve optimal clinical responses upon disease progression (retreatment or maintenance) is currently underway.

The success of ipilimumab has paved the way for the development of other immunotherapeutic agents that target immune checkpoints.[31] Programmed cell death 1 (PDCD1, best known as PD-1) receptor, for example, is a receptor expressed by T cells during long-term antigen exposure.[32] The interaction of PD-1

with its ligands, CD274 (best known as PD-L1) and PD-L2, which are highly expressed in the tumor microenvironment, inhibits T-cell activity. Of 135 patients treated with the anti-PD-1 monoclonal antibody MK-3475 in the context of a Phase I clinical trial, 38% had a confirmed response according to the Response Evaluation Criteria in Solid Tumors (RECIST). With 11 mo follow-up, response durations ranged from 2 to 11 mo, with most ongoing at the time of analysis.[33] In a Phase I study of nivolumab, another anti-PD1 antibody, 31% of 107 patients with advanced melanoma manifested an objective tumor response, the median duration of which was 24 mo. Long-term follow-up showed that median OS was 16.8 mo across all doses tested and 20.3 mo at the 3 mg/kg dose selected for Phase III investigations. Impressively, the 1-y and 2-y survival rates were 62% and 44%, respectively. With a median overall follow-up of 22 mo (range: 14–51 mo) 47 patients were still alive.[34]

Tumor Types Other than Melanoma

By targeting the immune system rather than malignant cells, the efficacy of immunotherapy is unlikely to be restricted by the tumor phenotype and/or genotype. For this reason, oncoimmunology has the potential to offer patients affected by many types of tumor the chance of long-term cancer containment, particularly as immunotherapeutic regimens are not subject to the resistance mechanisms associated with the use of targeted anticancer agents or conventional chemotherapy. However, based on data mining of exome sequencing, it is possible that tumor types with high rates of mutations could generate a wider T-cell repertoire than cancers presenting with few neoantigens.[35,36]

Data are accumulating from tumor types other than melanoma, including renal cell carcinoma (RCC) and lung cancer, primarily heralded by early phase clinical testing agents that inhibit the PD-L1/PD-1 signaling axis.[37,38] For example, among 34 patients with metastatic RCC treated with nivolumab at a dose of 1 mg/kg (n = 18) or 10 mg/kg (n = 16), 10 patients (29%) had an objective response and 9 achieved disease stabilization for at least 24 wk. In this setting, responses were durable, lasting a median time of 12.9 mo. Long-term follow-up showed that around half of all RCC patients (52%) were alive 2 and 3 y after the initiation of treatment. With long-term continuous dosing, the incidence of grade 3/4 related adverse events (AEs) was 21%, with no confirmed-drug related deaths or cases of severe pneumonitis.[39] Of 127 patients with non-small cell lung carcinoma (NSCLC) who received nivolumab at 1, 3, or 10 mg/kg, most of which were heavily pretreated (having received at least 2 lines of prior therapy), 20 patients (16%) manifested prolonged objective responses, and across all cohorts, median OS was 9.2 and 9.6 mo for patients with squamous (n = 73) and non-squamous NSCLC (n = 48), respectively. Remarkably, at the Phase III recommended dose of 3 mg/kg, median OS was not reached for patients with either histology. Survival was durable, with 44% and 41% of patients with squamous NSCLC alive after 1 and 2 y, respectively. Equivalent rates for patients with non-squamous NSCLC were 44% and 17%. The most common grade 3/4 AEs were fatigue, pneumonitis, and elevations in circulating liver enzymes.[40]

In a safety study of MPDL3280A, an inhibitor of PD-L1, 53 patients with RCC were treated at doses of 3 (n = 2), 10 (n = 12), 15 (n = 18), and 20 mg/kg (n = 21) for a median duration of 190 d. Grade 3/4 AEs attributable to treatment were reported in 13% of patients, with hypophosphatemia, fatigue, dyspnea, and hyperglycaemia being the most common. Among patients evaluable for efficacy (n = 39), durable objective responses, sometimes preceded by prolonged periods of disease stabilization, were observed across all doses.[41] Similarly, 53 patients with heavily-pretreated NSCLC were treated with MPDL3280A at doses of ≤ 1 (n = 2), 10 (n = 10), 15 (n = 19), and 20 mg/kg (n = 22) for a median duration of 106 d. Of these, 37 patients were evaluable for efficacy. Across all doses, an ORR of 24% (9/37) was observed in patients with squamous and non-squamous NSCLC, including several patients exhibiting rapid tumor shrinkage. All responses were ongoing or improving at the time of analysis.[42] In both these analyses, an apparent correlation was observed between PD-L1 expression status and response to MPDL3280A.

Updated results from a Phase I clinical trial testing MPDL3280A in 175 patients affected by various tumors (including RCC, melanoma, gastric cancer, breast cancer, sarcoma, and lymphoma), were presented at the European Cancer Congress, September 2013.[43] Objective responses were observed in all solid tumor types examined and the ORR was 21% with a 24-wk progression-free survival (PFS) rate of 42%. The 85 patients with NSCLC are the largest cohort of patients to be treated with PD-L1-blocking agents to date. All these patients were evaluable for safety and 53 of them for efficacy. Patients were heavily pretreated (almost half of them had had three lines of prior therapy), and 81% were current or former smokers. The ORR in the NSCLC cohort was 23% (similar to that of patients with adenocarcinomas or squamous cell carcinomas), and all responses were maintained for the duration of treatment (every 3 wk for a median 48 wk). Interestingly, the authors reported a higher ORR of 26% for patients who had ever been a smoker of cigarettes or cigars as compared with patients who had never smoked (ORR = 10%). The authors hypothesized that as compared with non-smokers, smokers might bear tumors with a high mutation rate, significantly increasing their immunogenicity.[44] Based on early evidence of activity, a number of Phase III clinical trials are ongoing in patients affected by different tumor types to confirm the clinical benefit derived from interrupting the PD-L1/PD-1 signaling axis.

Combinatorial Immunotherapy and Mixed Modality Combinations: A New Chapter

In preclinical studies, the concurrent administration of ipilimumab and nivolumab resulted in synergistic antitumor activity, providing the rationale for Phase I combinatorial study.[45] In this dose-escalation study, 69 pretreated patients with advanced melanoma were treated concurrently with nivolumab at 0.3, 1, or 3 mg/kg plus 3 mg/kg ipilimumab. Of 37 patients included in 3 completed cohorts, 14 (38%) had an objective clinical response according to modified WHO criteria. The clinical activity of the combinatorial regimen appeared to exceed that of either agent alone, with approximately 1-third of patients manifesting rapid

Table 1. Advantages and disadvantages of clinical trial endpoints in measuring treatment benefit

Endpoint	Definition	Advantages	Disadvantages
DCR	Number of patients with an objective response or SD of predetermined duration according to validated response criteria	• Demonstrates if treatment has a direct biological effect • Can be assessed in single-arm studies • Includes SD, which can be a clinically relevant outcome • Accounts for agents that work by cytostatic mechanisms	• Not statistically validated as surrogate for improved survival • Disease control may be transient • Length of SD required can vary among studies
HR	Comparison of survival at any point in time between two groups of patients	• Determines if difference between survival curves is statistically significant • Includes information from entire survival curve • Good indicator of relative benefit	• Assumes ratio remains constant over time
Landmark analysis	Number of patients alive at fixed time points after initiation of therapy	• Provides information on survival outcomes both before and beyond the median value, i.e., on the proportion of patients with early deaths or long-term survival • Informative data available with shorter follow-up than is needed for studies with median OS as the primary endpoint	• Not commonly implemented in trial designs • May not be appropriate for all drugs (depending on shape of survival curve) • Requires extended follow-up to generate long-term data

Mean OS	Area under the survival curve	• Reflects data from entire survival curve	• Finite follow-up means data must be extrapolated beyond point of last observed deaths
			• Assumptions must be made about
			  - Shape of the tail of the curve
			  - Effects of subsequent therapies

Median OS	Time point at which 50% of patients are expected to have survived	• Universally accepted as direct measure of benefit • Easily and precisely measured • Has value in terms of familiarity and consistency	• May involve larger studies • May be affected by crossover therapy and subsequent therapy • Includes non-cancer deaths • Does not convey differences in durability of survival, i.e., on patients who survive longer than median value
ORR	Number of patients with complete or partial tumor shrinkage according to validated response criteria	• Demonstrates if treatment has a direct biological effect • Trials require smaller patient numbers and are completed rapidly allowing early decisions to be made regarding future development • Can be assessed in single-arm studies • Doesn't include SD, which can reflect the natural history of disease	• Does not account for agents that work by mechanisms unlikely to cause tumor regression • Does not account for differences in response kinetics based on drug's mechanism of action • Responses do not necessarily translate into improved survival • Responses may be transient
PFS	Time from randomization until objective tumor progression or death Definition of tumor progression should be carefully detailed in protocol	• Smaller sample size and shorter follow-up than needed for survival studies • Includes SD, which can be a clinically relevant outcome • Not affected by crossover or subsequent therapies • Generally based on objective and quantitative assessments	• Not statistically validated as surrogate for survival in all settings • Not precisely measured • Subject to assessment bias particularly in open-label studies • Definitions vary among studies • Frequent radiological or other assessments required • Limited utility in cases of durable post-progression survival

Abbreviations: DCR, disease control rate; HR, hazard ratio; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; SD, stable disease.

and profound tumor responses (≥ 80% tumor reduction at week 12), and prompt resolution of symptoms. In fact, at the dose levels chosen to move forward with (1 mg/kg nivolumab plus 3 mg/kg ipilimumab), 100% of treated patients (n = 9) had a reduction of tumor volume ≥ 80% from the initiation of treatment. Responses to the combinatorial regimen were durable, ranging from approximately 6 to 100 wk at the time of analysis. Importantly, the combination of nivolumab and ipilimumab had a manageable safety profile. Although some AEs related to concurrent treatment were increased in frequency, they were similar in nature to those typically seen with monotherapy and could be managed using standard protocol algorithms.[46,47]

Combinatorial approaches based around checkpoint inhibitors have the potential to improve clinical outcomes, and given that the relationship between the immune system and tumor microenvironment is so complex, the number and type of possible combination is extensive. For example, checkpoint inhibitors could be combined with other immunostimulatory agents such as Toll-like receptor, CD28, tumor necrosis factor receptor superfamily, member 9 (TNFRSF9, best known as CD137) or TNFRSF9 (best known as OX40) agonists,[48,49] as well as with cytokines such as IL-2, IFNα, or granulocyte macrophage colony-stimulating factor (GM-CSF).[50,51] Alternatively, given their distinct mechanisms of action, checkpoint inhibitors could be used in combination with conventional drugs including targeted anticancer agents;[52] cytotoxic chemotherapeutic that induce immunogenic cell death,[53,54] or radiotherapy.[55]

Most of the responses seen with checkpoint inhibitors occurred by the time the first imaging was performed, i.e., 8 or 12 wk after the initiation of treatment. Rapid and robust responses such as these are akin to those commonly observed with targeted anticancer agents. However, whereas the responses to targeted therapies are often limited in duration due to the surge of resistance, the indirect activity of immunotherapies allow them to elicit long-lasting responses. This suggests that when measuring the true benefit of treatment, it is not enough to simply determine the proportion of patients with an objective response or tumor control. Now, the quality of this outcome in terms of durability must also be considered, as long-lasting tumor control may translate into long-term patient survival.

Is There a Need to Redefine Treatment Goals?

For many years, the primary aim of therapies against advanced cancer was to reduce tumor burden and palliate symptoms, and treatment success was traditionally measured by response rates, median PFS and, as the gold standard, median OS (**Table 1**). In oncology, many different measures are used to represent survival outcomes. Although limited by the maximum duration of follow-up within a given study, differences between Kaplan–Meier survival curves can be used to provide information on survival in a number of ways. Median OS uses both axes to determine the time point at which 50% of patients are expected to have survived and is reported as the primary endpoint in many cancer treatment studies. It therefore has value in terms of both familiarity and consistency. However, median OS is a snapshot comparison of a single time point and thus provides a limited measure of benefit. In particular, differences in the durability of survival, i.e., information on those patients that may survive longer than the median value, are not conveyed.[56,57] Additionally, log-rank tests are used to determine if the difference observed between 2 survival curves at a certain time point is statistically significant. Results are expressed as a HR, whereby "hazard" is defined as the probability of death at a certain time. The HR between treatment arms is a good indicator of relative benefit and includes information from the entirety of the Kaplan–Meier analysis. HRs are a more precise way of reporting survival outcomes than median values. Furthermore, clinicians and patients are more likely to support or accept treatments based

on relative increases in survival rather than absolute differences in the number of patients alive at a single timepoint.[57,58] Calculating the HR, however, assumes that the ratio remains constant with time, which is not always the case.

The plateau in survival that has been observed with immunotherapeutic agents such as sipuleucel-T, a therapeutic vaccine against prostate cancer,[59] as well as ipilimumab,[60] appears to be maintained for an extended period, suggesting that if patients survive at least 2 or 3 y from the start of treatment, they have a better chance of living a long time, even with metastatic disease.[27] Now that long-term survival has become a realistic treatment goal, traditional endpoints used in clinical trials may no longer fully describe the potential survival benefits being achieved. Instead, endpoints that better correlate with prolonged survival, including durable disease control, as well as landmark survival analyses and quality of life endpoints are becoming more relevant.

Perhaps the best measure of whether a treatment can provide long-term clinical benefit comes from landmark analyses of survival performed at fixed time points after the initiation of therapy. In these analyses, patients are identified as survivors if alive at a pre-specified time point and all patients who die or are censored prior to the selected "landmark" time are not.[61] Landmark analyses quantify absolute differences in survival at multiple time points, e.g., 1, 2, 3 y and beyond, thus demonstrating the number of patients with long-term survival (≥ 2 y) and the duration of survival. An important consideration is whether patient-reported outcomes should also be incorporated into these measures as a means of understanding not only how much a patient's life is extended, but also the quality of the additional time obtained from treatment.

Conclusions

The development of ipilimumab for the treatment of advanced melanoma has served as the foundation for immunotherapy, providing important insights into the potential for this approach to provide long-term tumor control and extend patient survival. As immunotherapeutic approaches are established as one of the pillars of anticancer treatment, the next stage will be to determine how the existing knowledge and expertise might be extended to patients with malignancies other than melanoma, if not all tumor types.

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