Cachectic Cancer Patients: Immune to Checkpoint Inhibitor Therapy?
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Immune checkpoint inhibition is dramatically improving patient outcomes in diverse cancers, many of which responded poorly to traditional cytotoxic agents. Drivers of heterogeneous response to immune checkpoint therapy are poorly characterized. Cachectic cancer patients exhibit high CL0 patients leading the authors to hypothesize that underlying disease involvement and cancer cachexia may be confounding the exposure–response relationship to pembrolizumab. In other words, high therapeutic antibody clearance in the presence of elevated patient catabolism appears to be a marker of refractory disease, rather than a cause for therapy failure; as a result, cachectic cancer patients appear refractory to pembrolizumab.

Cachexia, or involuntary and often extreme loss of bodyweight, has been a well-recognized feature of advanced malignancy for millennia, but only recently has a consensus definition emerged for cachexia in the context of cancer (2). Inherent to this definition, and distinct from simple starvation, is the fact that cachectic wasting cannot be reversed with appropriate nutritional support. Malnutrition is a frequent result of cancer progression and therapy and undoubtedly contributes to cachectic decline. It is currently unclear when generally malnourished cancer patients transition to cachexia that is refractory to aggressive nutritional support. However, both malnutrition and cancer cachexia are associated with a procatabolic state that remains poorly understood by those providing cancer therapy and is the subject of robust ongoing research efforts. Turner and colleagues point out that this procatabolic state, often characterized by hypoalbuminemia, could explain elevated pembrolizumab CL0. In fact, this is a standard assumption made by pharmacologists studying antibody therapies that dysregulated protein breakdown mechanisms driving skeletal muscle decay likely overlap with those same processes clearing exogenous and endogenous serum proteins (3). However, the authors’ analyses reveal that while delivering increased pembrolizumab to correct for this increased CL0 does in fact increase drug exposure, the increased exposure does not translate to improved outcomes. The data suggest the procatabolic patient displays primary resistance to pembrolizumab (Fig. 1).

In an effort to understand why patients with elevated protein catabolism fail to respond to pembrolizumab, seemingly over a wide range of drug exposure, the authors point to recent work linking metabolic dysfunction and immune suppression demonstrated in cachectic mice (4). The studies show that heightened circulating IL6 results in the suppression of PPAR-alpha (PPARα)–mediated ketogenesis within the liver of cachectic animals, further triggering systemic glucocorticoid release as part of an appropriate biologic response to metabolic stress.

In two large clinical trials, the investigators report a seemingly paradoxical association between rapid baseline plasma clearance (CL0) of pembrolizumab and poor overall survival (OS), despite a lack of association between plasma exposure and OS at doses between 2 mg/kg and 10 mg/kg. They also note dose-proportional pembrolizumab pharmacokinetics yet a large within-dose variability in OS. These findings are consistent with previous reports of significant percentages of patients failing to respond to immune checkpoint therapy despite ample expression of relevant targets. Yet, this study goes a crucial step further in identifying features of poorly responding patients. Despite having roughly 5-fold higher systemic exposure, high CL0 patients receiving 10 mg/kg pembrolizumab had similar poor outcomes as high CL0 patients receiving 2 mg/kg pembrolizumab. At both doses, patients with low CL0 exhibited a remarkable 15-month advantage in OS compared with patients with high CL0. The relationship between CL0 and survival was observed in both advanced melanoma (n = 211) and advanced previously treated non–small cell lung cancer (NSCLC, n = 537) and persisted even after correcting for established baseline clinical risk factors. In both populations, on-study reductions in patient body weight and serum albumin were associated with reduced survival in high CL0 patients leading the authors to hypothesize that underlying disease involvement and cancer cachexia may be confounding the exposure–response relationship to pembrolizumab. In other words, high therapeutic antibody clearance in the presence of elevated patient catabolism appears to be a marker of refractory disease, rather than a cause for therapy failure; as a result, cachectic cancer patients appear refractory to pembrolizumab.

In this issue of Clinical Cancer Research, Turner and colleagues (1) reveal how patient’s protein metabolism dramatically impacts the therapeutic efficacy of pembrolizumab, a humanized IgG4 mAb and immune-checkpoint inhibitor that binds directly to programmed cell death 1 (PDCD1). Unlike small-molecule xenobiotics, the catabolism and clearance of pembrolizumab interfaces with a complex and highly orchestrated host protein intermediary metabolism, which displays high rates of dysfunction in patients with cancer.

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Therefore, cachectic mice and likely cachectic humans with elevated circulating IL6, exhibit some degree of glucocorticoid-mediated immune suppression resulting in limited T-cell chemotaxis and poor response to immune checkpoint inhibition. This hypothesis was nicely validated by recent studies in murine models of pancreatic ductal adenocarcinoma (PDAC) where concurrent IL6 blockade with PD-L1 (CD274) targeted therapy resulted in improved overall T-cell activation and antitumor response (5). Anti-IL6 therapy has failed to demonstrate any clinical benefit in cachectic patients, but these studies suggest successful blockade of the IL6 axis in the cachectic liver could restore homeostatic nutrient utilization and reduce immune-suppressive glucocorticoid release. Importantly, the effects reported in cachetic animals largely parallel the long-known association between protein–calorie malnutrition and poor immune response to many types of stimuli (4).

The use of elevated mAb Cl0 as an early marker for ongoing malnutrition or cachexia offers an opportunity for intervention that may improve responses to potentially highly effective drugs. There remains intense interest in discovering improved biomarkers of cancer cachexia and malnutrition to facilitate early deployment of nutritional support, guide disease management decisions, and more precisely study the efficacy of anticachexia interventions. Although balanced for other clinical features at enrollment, Turner and colleagues have shown that high Cl0 of pembrolizumab was predictive of the subsequent development of cancer wasting in advanced NSCLC and melanoma populations. This suggests that rapid clearance of pembrolizumab, and potentially other mAb therapy, could serve as an indicator of a high-risk population suffering from malnutrition and subclinical cachexia or precachexia. Research is needed to address how these findings may be deployed in an oncology clinic, but in the context of early-phase clinical trials, patients with rapid mAb Cl0 warrant close scrutiny based on their cachetic potential.

The study by Turner and colleagues provides evidence that patients experiencing elevated serum protein catabolism are refractory to at least one class of immune checkpoint inhibitor therapies that are revolutionizing the management of multiple cancers, many of which coincide with high rates of malnutrition and cachexia (2). The strategy to address this issue and improve therapeutic responses is necessarily multidimensional and must include research on appropriate screening, new biomarkers, and novel antiwasting interventions. The merits of developing specific anticachectic therapies have been historically debated based on the notion that effective antineoplastic therapy will also reverse cachectic decline, whereas, the likely impact of effective anticachectic intervention on cancer burden and patient survival are unclear. Advocates for treating cachexia have been hopeful that effective anticachexia intervention would fortify the cancer patient such that more aggressive and hopefully effective anticancer therapy could be pursued to improve both quality and quantity of life. Turner and colleagues have shown that in addition to well-characterized reductions in patient tolerance to cytotoxic therapy, malnutrition and/or cancer cachexia is directly associated with pembrolizumab resistance. Furthermore, they highlight similar patterns in data reported for nivolumab, atezolizumab, and ipilimumab, suggesting a more general relationship between a procatabolic state and poor response to immune checkpoint inhibitors.

When the composite effects of malnutrition and cachexia on anticaner therapy are expanded to include primary therapeutic resistance to immune-check point inhibition in addition to increased treatment-related and often dose-limiting toxicities, the need for accurate patient assessment and effective antiwasting interventions is clarified. It appears increasingly unlikely that the potential benefits of antibody therapy will be fully realized without addressing the underlying critical host metabolic dysfunction. After decades of intense study, scientists and clinicians are translating knowledge regarding the highly orchestrated anticancer immune response into meaningful and broadly applicable strategies to improve outcomes with durable responses and potential cures. The work by Turner and colleagues provides greater insight and a clear conclusion that we must also focus upon patient nutritional status, metabolism, and cancer cachexia in order to maximize the benefit of immunotherapy.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.
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