PALLIATIVE CARE NETWORK OF WISCONSIN

FAST FACTS AND CONCEPTS #445
OUTCOMES OF IMMUNE CHECKPOINT INHIBITORS IN PATIENTS WITH CANCER AND A POOR PERFORMANCE STATUS

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Background: Several immune checkpoint inhibitors (ICIs, also referred to as immunotherapy) (see *Fast Fact* #277) are approved as monotherapy or in combination with other systemic therapy for treating advanced malignancies (1,2). The ability of ICIs to generate durable responses in advanced cancers resistant to traditional cytotoxic chemotherapy formed the basis of the 2018 Nobel Prize in Medicine (1-3). Their use has skyrocketed in cancer care, with a large proportion of their use in patients with a poor performance status (PS) for whom outcomes are less clear since they are often trial ineligible. This *Fast Fact* will review the available data and care strategies of ICIs in patients with cancer and a poor PS.

Impact of PS and comorbidities: Poor PS is often defined as an Eastern Cooperative Oncology Group (ECOG) PS of 2 or greater or a Karnofsky PS (KPS) of 60 or less (4-6). A poor PS is strongly associated with negative predictive factors for response, morbidity, and mortality from cytotoxic chemotherapy (see *Fast Facts* #416 and 434). However, ICI are more tolerable than standard chemotherapy with less associated nausea, vomiting, fatigue, and myelosuppression reported (6). Thus, ICIs commonly are offered to patients felt to be too high risk for cytotoxic chemotherapy due to a poor PS (7), even though the inclusion criteria for most randomized clinical trials of ICIs excluded or underrepresented patients with organ dysfunction, autoimmune disease, a poor PS, age greater than 65, or central nervous system metastases (4,5,8,9). Collectively, this is a large proportion of cancer patients in the US (8).

Impact of prognostic uncertainty: There are many prognostication challenges for those being considered for ICI. In addition to the limitations in the published evidence regarding ICI outcomes for those with a poor PS, there is the possibility of "exceptional responders" (9). Exceptional responders have been defined as a small fraction of patients (e.g., less than 10% of similar patients), who experience a partial or complete response (10). These "exceptional" responses can be so durable in select cases that they are challenging the conventional view of metastases being a sign of incurability for solid cancers (9). Identifying who is appropriate for ICI and who is an appropriate for hospice care is also becoming more complex for patients, families, and clinicians who are often trying to set reasonable expectations of future trajectories and goals of care. Coordinated discussions with the treating oncology teams are imperative when generalist clinicians are facing this dilemma.

Outcomes in patients with cancer and a poor PS: To date, few trials offer a comparison between patients with a good PS (ECOG 0 to 1) to a poor PS (ECOG 2 or greater). Indirect data show:

- Patients with bladder cancer experienced a significant survival advantage for pembrolizumab in the overall and good PS cohorts, but not in the small subset (n=6) with an ECOG of 2 or worse (11).
- In a prospective study evaluating nivolumab for patients with metastatic non-small cell lung cancer, patients with an ECOG of 2 had an overall survival of 3.9 to 5.4 months compared with 9.9 to 10.5 months for those with a good PS (12),
- Retrospective data show similar findings (4,13). The largest included a cohort of 30,000 patients with lung, bladder, kidney, and liver cancer. Median overall survival was 10 months shorter in patients with a poor PS and nearly 40% with a poor PS who received ICI treatment died within 6 months (4).

Adverse effects and outcomes from ICI in those with a poor PS: Real-world data suggest adverse events from ICIs are higher than in clinical trials (e.g., pneumonitis in 19% vs 3% reported in trials). This is likely because in practice more patients with comorbidities and/or a poor PS receive ICIs. These adverse events (see *Fast Facts* #375) can range in severity and reversibility. Some are mild, others are associated with significant reduction in organ function, quality of life and length of life. Additionally, ICI treatment is associated with lower hospice enrollment, more inpatient deaths, more financial toxicity (see *Fast Fact* #409), and more life-prolonging treatment during the last month of life (15-19).

Navigating the unknown: Clinicians involved in the care of patients with a poor PS (or organ dysfunction) who are being considered for ICI therapy should understand the impact PS has on their

prognosis and the complex dynamics involved in their care. The following clinical pearls should help generalist clinicians navigate them:

- Re-evaluate PS each clinic visit and identify those who have gone from a "good" to a "poor" PS.
- Leverage this information when eliciting the patient's prognostic understanding and care preferences to ensure they align with their cancer clinician's goals and reasonable expectations of ICI therapy.
- Instead of seeking and/or committing patients to dichotomous treatment goals and/or plans of care (e.g., comfort-only care or life prolonging care without treatment limitations), focus initial visits on providing anticipatory guidance on common trajectories of illness and ICI treatment.
- Utilize coping strategies such as "hope for the best, prepare for the worst" or "best case/worst case" clinical decision-making models to prepare for the potential for contradictory responses (20,21).
- Provide multi-dimensional support from an interdisciplinary team involving chaplains, social workers, psychologists, etc, to alleviate distress from facing an unknown future.
- Consider care resources that can offer support for patients facing potentially dichotomous outcomes. For example, home or community palliative care or open-access hospice may allow the patient to access robust care and support while undergoing ICI as a time-limited trial.

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