Hope Before the Data Catch Up

On the ninth floor of Duke University Hospital are our inpatient cancer wards. I don't attend on the solid tumor service anymore, but I still recall the debilitating effects of cancer on the people there—their suffering and dying. On the walls between the hospital wings hang some paintings and a few framed poems meant to lift the spirits of the staff and family members who pass by. Years ago, I noticed one of the poems, "When I Heard the Learn'd Astronomer" by Walt Whitman. First published in 1865 and added to his masterpiece *Leaves of Grass* in 1867, the poem recounts the narrator attending a scientific presentation about astronomy:

> When I heard the learn'd astronomer,
> When the proofs, the figures, were ranged in columns before me,
> When I was shown the charts and diagrams, to add, divide, and measure them,
> When I sitting heard the astronomer where he lectured with much applause in the lecture-room,
> How soon unaccountable I became tired and sick,
> Till rising and gliding out I wander'd off by myself,
> In the mystical moist night-air, and from time to time,
> Look'd up in perfect silence at the stars.

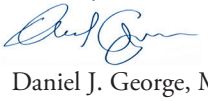
Over the years, I have read this poem with different interpretations. Early in my career, I felt disrespected by the writer, who seemed unappreciative of the hard work of scientific research. Later, I came to appreciate the poem as a testament to the limitations of science, the incomprehensible complexities of astronomy (or in our case, cancer), and how humbling it is to be a cancer researcher. More recently, I have come to appreciate a new perspective. Wandering off by myself and letting my thoughts roam, I have become comfortable with the unknowns in life and even draw upon them for inspiration. The limits of our scientific knowledge should not close our minds to the possibility that, with time, certain patients will benefit even more than we expect from our current treatments. It is this hope that our patients are counting on.

I recently saw for a second opinion a patient who was in need of hope. He had been successfully treated for stage I bladder cancer and was in remission, only for an incidental single liver metastasis to appear five months later. With no other sites of cancer, he started treatment with enfortumab vedotin and pembrolizumab, which had doubled the median overall survival in comparison with standard chemotherapy in the EV-302 trial. After about 6 months of treatment, his tumor had shrunk by half, and he was referred for possible consolidative surgery. I told him that we could use his tumor response as an indicator of response in any potential microscopic disease elsewhere, and that once his tumor response had stabilized, we should consider additional tumor-directed therapy for his residual liver lesion. He said he understood this plan and asked about his prognosis.

First, I told him that his circumstances were extremely unusual; stage IV disease rarely develops in patients with stage I bladder cancer without some local growth as well, and rarely does their cancer manifest with just one liver metastasis. Second, I described the clinical data with this regimen. Given how well his cancer had responded to therapy and the lack of long-term data with the regimen, there was reason to hope that further treatment might lead to cure. He thanked me for my explanations and my expression of hope. He told me that his primary oncologist had told him that the goal of therapy was to extend his survival, but that he would eventually die of cancer. I reassured him that he had received excellent care, and there was a chance he could fall into a subset of patients who might experience a long-term remission.

Extended follow-up of phase 3 clinical studies is not required for most approvals of cancer drugs, but patients and cancer practitioners desperately need these data. In advanced kidney cancer, CheckMate 214 initially reported an overall survival benefit in favor of ipilimumab and nivolumab in comparison with sunitinib after just 2 years of follow-up, leading to FDA approval. When the authors reported their 8-year follow-up data, they not only confirmed this overall survival advantage but also revealed that 25% of the patients treated with ipilimumab and nivolumab were still alive and free of disease progression, in comparison with just 8.5% of the patients treated with sunitinib, despite the fact that most patients had stopped therapy after 2 years. This 25% tail of the curve offers hope of long-term remission that would never have been known without extended follow-up. Maybe we will see a similar effect in bladder cancer from the EV-302 trial in the years to come. But until then, offering hope in the absence of long-term data is perhaps the most humane way to address this unknown.

Sincerely,



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