CLINICAL VIGNETTE

Melanoma: Treatment Considerations and Challenges in the Elderly

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Case Presentation

A 94-year-old male with a history of sun-damaged skin and previously excised cutaneous melanoma presented with a 2 cm plum-colored nodule on his right upper back. A shave biopsy was positive for an ulcerated superficial spreading melanoma. It was Clark's level 4, negative for the BRAF mutation, with brisk tumor- infiltrating lymphocytes. Within three weeks he had progressive disease with re-growth of tumor to 4 cm. and re-excision was performed which showed positive margins. The patient experienced rapid progression of subcutaneous nodules on his back and was referred to Oncology. At the time of presentation he had 25 % involvement of his back with nodules that were ulcerated and bleeding. Staging workup with PET/CT revealed hypermetabolic subcutaneous nodules in the right lower neck, right upper back and right shoulder with standardized uptake value (SUV) maximum of 12.2. He also had right axillary and subcarinal adenopathy. MRI of his brain showed no evidence for metastatic disease.

Discussion

The incidence of melanoma increases with age, and so it is not unusual to make treatment decisions in the very elderly. The American Cancer Society estimates for the year 2020, more than 100,000 Americans will be diagnosed with cancer, 60% in men and 40% in women.[1] Data from 2012 – 2016 indicate significantly increased cases among non-Hispanic white males aged 60 – 64 years and 70 – 74 years.[2]

Superficial spreading malignant melanoma is the most common of the four major subtypes and comprises about 75% of all melanomas. It can occur in any anatomic location and at any age but seems to have a predilection for the back in men and the lower extremities in women.

At diagnosis, elderly melanoma patients present with thicker and more frequently ulcerated tumors compared with younger patients. These features; may result from longer delays in diagnosis which can occur for a variety of reasons. The elderly may have greater difficulty participating in screening programs, lack access to medical care, or have issues with cognitive impairment, diminished vision, depression and isolation.[3] These factors impact on overall survival, as stage of disease at diagnosis is an important prognostic factor.

Historically patients with advanced or metastatic disease had a poor prognosis with overall survival less than one year. However, newer treatments with immunotherapy and targeted agents have revolutionized opportunities for patients to have sustained long-term survival.

Ipilimumab, a monoclonal antibody directed against CTLA-4 was the first treatment to yield improved overall survival and durable responses in patients who had progressed on other therapies.

In August of 2010 the NEJM reported the results of a phase III randomized study showing that ipilimumab alone or with a glycoprotein 100 (gp100) vaccine improved overall survival compared with the vaccine alone in patients with previously treated metastatic disease. Median overall survival improved to 10.1 months compared to 6.4 months[4] The Food and Drug Administration approved Ipilimumab on March 25, 2011 for advanced or metastatic melanoma in patients who no longer respond to standard therapy. This was the first of emerging therapies in checkpoint blockade.

Four years later, July 2015, the NEJM published the results of a randomized double-blind phase III study comparing nivolumab alone or nivolumab + Ipilimumab to ipilimumab alone in patients with unresectable Stage III or Stage IV metastatic melanoma in the first line setting.[5] Eligible patients had histologically confirmed stage III (unresectable) or stage IV melanoma and had received no prior therapy. Eligibility criteria included an ECOG performance score of 0-1. The patients were well-stratified according to age, sex, ECOG performance score, stage of disease programmed death-ligand 1 (PD-L1) status and BRAF status.

Of the total number of patients stratified N =945: (59 %) were < 65 years, (27%) were 65– 75 years and (12%) > 75 years The oldest patient was 90 years of age.

The results showed that among previously untreated patients with metastatic melanoma, Nivolumab alone or combined with Ipilimumab showed significantly longer progression free survival.

The first survival outcome report was published October 2017 in the NEJM. The overall survival rate at 3 years was 58% in the nivolumab + ipilimumab group and 52% in the nivolumab group, as compared with 34% in the ipilimumab group.

The safety profile at 3 years was unchanged from the initial report. Treatment-related adverse events of grade 3 or 4 occurred in 59% of the patients in the nivolumab + ipilimumab groups, in 21% of those in the nivolumab group, and in 28 % of those in the ipilimumab group.[6]

The latest updated survival outcomes were reported last year. Overall survival at 5 years was 52% in the nivolumab-plus-ipilimumab group and 44% in the nivolumab group as compared with 26% in the ipilimumab group.[7]

Although this landmark study included elderly patients, greater than 80% of the patients were younger than 75 years.

We have limited prospective data about the activity of immune checkpoint inhibition in the very elderly. Ciccarese et al published a systematic review and meta-analysis of the anticancer efficacy of immune checkpoint inhibitors according to patient's age. Twenty-nine randomized clinical trials totalling 18,839 patients were included in the systematic review. The majority of the studies defined "young" as patients less than 65 years (n= 10,832), and "elderly" as patients aged 65 years and older (n= 7723); Seven studies identified a third subgroup of very elderly patients aged 75 years and above (n= 421)

In both young and elderly patients with advanced cancers, regardless of the tumor type, immune checkpoint inhibitors significantly improved overall survival. The magnitude of benefit is debated in patients aged 75 years and older.[8]

Our 94-year-old patient had a detailed discussion regarding the potential benefit and known risk of adverse events of immunotherapy. He was living independently and had no significant comorbidities. He was quite symptomatic from his disease and was eager to be treated. We elected to give him single agent therapy with nivolumab as this is better tolerated than the combination of ipilimumab and nivolumab.

His interim PET/CT showed marked improvement and near-complete resolution of all subcutaneous disease. He continues on treatment and is nearing his one-year anniversary.

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