Case report

Should age disqualify from life-prolonging therapy? Successful adjuvant immunotherapy in an 88-year-old octogenarian with melanoma and high cardiovascular risk

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ABSTRACT

Advanced chronological age should not automatically lead to patients' disqualification from cancer therapies, which have the potential to prolong life. When functional status is prioritized over metric age, even octogenarians with significant comorbidities can have access to even modern oncological therapies. We present the case of an 88-year-old patient with high cardiovascular risk, who was enrolled in adjuvant nivolumab therapy due to melanoma recurrence. In 2021, the patient was diagnosed with malignant melanoma of the lumbar region at stage T2a, which was initially successfully surgically treated. After 3 years, regional melanoma recurrence in the axillary lymph nodes was detected (stage III, BRAF-) indicating the necessity for systemic treatment. During cardiological consultation before planned immunotherapy, severe aortic stenosis was confirmed. The patient finally was qualified for nivolumab therapy under cardio-oncological supervision, despite advanced age and high cardiovascular risk. After 5 courses of immunotherapy, no recurrence was found on follow-up computed tomography, and no cardiac status worsening was observed. This case demonstrates that advanced age combined even with high cardiovascular risk should no longer be a barrier to immunotherapy under an appropriate monitoring protocol preserving the safety and continuity of oncological treatment.

Key words: octogenerians, melanoma, immunotherapy, aortic stenosis, cardiooncology

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INTRODUCTION

Melanoma is a malignant skin cancer whose incidence is strongly correlated with the aging process. It poses a particular diagnostic and therapeutic challenge among elderly patients. Epidemiological analyses alarm that people over 80 years of age (octogenarians) have the highest risk of death from cancer, which is often associated with treatment skepticism based on chronological age [1]. Regardless, a knowledge gap persists in geriatric oncology, as the oldest old, especially with comorbidities, have been systematically excluded from randomized controlled trials. This has led to gaps in the evidence regarding the efficacy and safety of modern therapies in the oldest patient group and hinders the formulation of evidence-based recommendations [2, 3]. Currently, the standard of adjuvant treatment for stage III melanoma following radical resection is immunotherapy using immune checkpoint inhibitors (ICIs), such as nivolumab. According to the CheckMate 238 trial, significant improvement in recurrence-free survival (RFS) was observed with this therapy. Over half of the patients (51,7%) receiving nivolumab remained RFS after 4 years [4]. Guidelines suggest personalizing treatment, noting that chronological age should not, in itself, be a contraindication to modern therapies [5]. Currently, the basis for decision-making should not be the date of birth alone, but rather a geriatric assessment that considers performance status (PS) as evaluated by applying standardized scales, such as the Karnofsky Performance Scale (KPS) or the Eastern Cooperative Oncology Group scale (ECOG) [6]. Additionally, multimorbidity may influence decision-making about initiating ICIs, so cardio-oncology guidelines recommend systematic cardiovascular risk assessment to ensure a safe immunotherapy procedure, especially patients with high cardiovascular disease [7]. Proactive clinical vigilance is critical due to ICIs-related cardiotoxicity. Although rare, cardiotoxicity occurs several times more frequently in real-world data than in clinical trials and often has a rapid, potentially fatal course [8]. This paper presents the case of an 88-year-old patient with severe aortic stenosis who was successfully treated with adjuvant nivolumab under close cardio-oncological supervision. This case illustrates that advanced chronological age combined with significant cardiac comorbidities should not automatically disqualify a patient from potentially life-prolonging treatment.

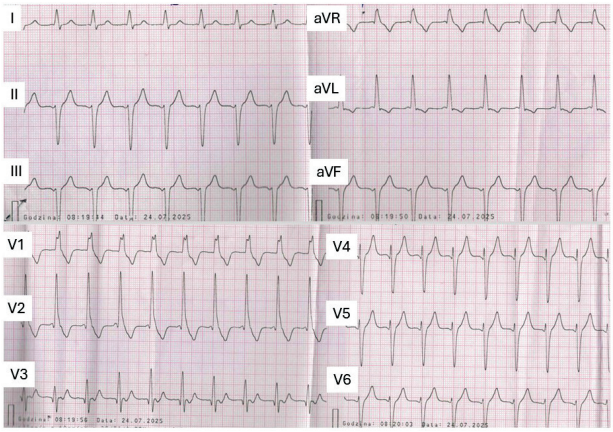
CASE REPORT

In 2021, the 84-year-old male patient (80 on KPS) was diagnosed with malignant melanoma of the right lumbar region, which was successfully surgically treated. Histopathological examination of the lesion revealed malignant melanoma: T2aN0M0; clinical stage IB. This result was an indication for radicalization, and a sentinel lymph node biopsy was performed in 2022 – the result was negative, and observation was recommended. In December 2024, a fine-needle aspiration biopsy revealed metastases in the right axillary lymph nodes. Based on these results, 4 months later, lymphadenectomies in these areas were performed, and metastasis was detected in 1 of 11 examined lymph nodes (stage III), confirming late regional recurrence. Due to the absence of BRAF gene mutation, adjuvant therapy with nivolumab was planned. Given the planned ICIs administration and the patient's advanced age, a comprehensive cardio-oncological consultation was ordered to assess cardiovascular risk.

Medical history revealed hypertension (treated with combined drug – perindopril 10 mg with indapamide 2.5 mg once daily) and malignant prostate cancer (cT2aN0M0, clinical stage I) undergoing exclusively gonadotropin-releasing hormone analogue therapy (leuprolide acetate, 45 mg every 6 months). Most importantly, the patient reported also severe aortic stenosis with no decision on surgical treatment, probably due to asymptomatic course.

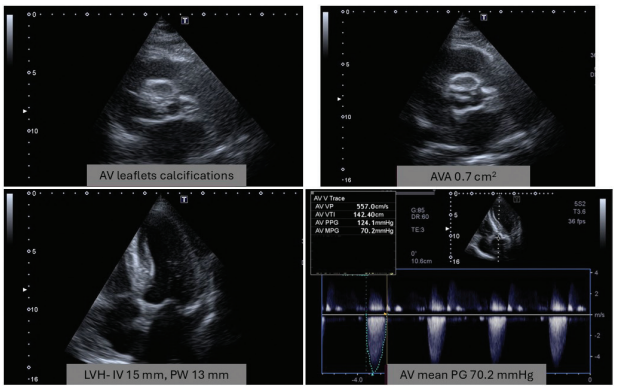
Despite advanced age and valvular disease, the patient was in very good physical condition (KPS 80), reporting even skiing several months before. On physical examination, the systolic murmur in the aortic valve area was noted, no signs of cardiac decompensation. Blood pressure was 120–130/80 mmHg at home measurements. The electrocardiography (ECG) showed a regular sinus rhythm of 100/min, left axis deviation, right bundle branch block, signs of left ventricular hypertrophy, and negative T waves in lead aVL (fig. 1). On echocardiography, left ventricle was not dilated (diastolic diameter 46 mm), with signs of hypertrophy (septum on diastole 15 mm, posterior wall on diastole 13 mm). Left ventricular ejection fraction was 55%, without segmental contractility disorders. The high-grade aortic valve (AV) stenosis was present with massive calcifications of 3 aortic leaflets with their limited separation up to 5 mm. The transaortic AV maximum pressure gradi-

Figure 1. Electrocardiogram of the patient revealing signs of left ventricular hypertrophy and right bundle branch block.



ent was 124 mmHg, the mean gradient was 70 mmHg and aortic valve area (AVA) was 0.70 cm^2, confirming the diagnosis of severe aortic stenosis (fig. 2). Laboratory tests showed a mildly elevated baseline troponin level of 26 pg/mL (normal range <14 pg/mL). The patient was qualified for ICIs but was classified with high cardiovascular risk. Therefore, cardiac monitoring including control ECG and troponin tests before each ICIs administration were recommended. The patient began immunotherapy with nivolumab (i.v., 480 mg every 28 days).

Figure 2. Echocardiography of the patient showing critical high-grade aortic stenosis. A left ventricle hypertrophy (LVH) with thickened interventricle septum (IV) and posterior wall (PW) with massive calcifications of aortic valve (AV) leaflets, reduced aortic valve area (AVA) and increased AV mean pressure gradient (PG) could be noted.



After the fifth treatment cycle, the first full assessment of results was performed. On clinical examination, the patient was still 80 on KPS, reporting only occasional dyspnea with stable troponin level and no significant changes on echocardiography. Complete blood count, kidney and liver parameters were within normal limits. A follow-up computed tomography scan of the central nervous system, chest, abdomen, and pelvis showed a stable image with no signs of spread. The patient was qualified to continue nivolumab therapy with continued cardio-oncological monitoring.

DISCUSSION

ICIs may be an especially promising treatment for older patients because they have no contraindications for pre-existing organ dysfunction and a milder toxicity profile compared to traditional cytotoxic cancer therapies [9]. Although ICIs targeting programmed cell death protein 1 (PD-1) have limited efficacy and safety data among the oldest patients – existing data are promising. ICIs effectiveness among octogenarians is also the subject of intensive research due to an age-associated decline in immune function known as immunosenescence, which in theory, could limit the effectiveness of these drugs. However, the observation that ICIs could be effective at older age may be supported by the higher rate of tumor mutations in seniors, which paradoxically makes them more responsive to immunotherapy [9]. A multicenter cohort study involving patients aged 80 years or older showed that ICIs' potency in this group is comparable to that in younger groups, and they have an acceptable toxicity profile [3]. Another meta-analysis confirmed the benefits of anti-PD-1 therapy in patients aged ≥75 years in both first- and second-line settings [10]. Data from real-world evidence of melanoma in patients aged ≥75 years (n = 456) treated with adjuvant pembrolizumab or nivolumab showed that effectiveness in the older group is comparable to that observed in clinical trials of younger patients [11]. These studies have confirmed that age should not be an individual criterion for excluding patients from such treatment [3, 9, 10]. In clinical setting however, subjective concerns about toxicity can still lead to the situation where the oldest can be excluded from the modern treatment, although data from real clinical practice indicate that the incidence of adverse events remains statistically comparable to that in younger populations. However, it should be remembered that due to limited organ reserve in older adults, even minor complications call for careful clinical monitoring [3].

In the case of the 88-year-old described patient, the key eligibility criterion was the PS assessment, rather than chronological age alone. The patient had a score 80 in KPS, which indicates normal activity with minimal disease symptoms. Meta-analyses have shown that PS is a stronger prognostic factor for immunotherapy efficacy than age [12]. Studies have also noted the value of a comprehensive geriatric assessment in making therapeutic decisions for older cancer patients receiving ICIs [11]. Such an approach is in accordance with the guidelines that recommend adjuvant immunotherapy for stage III melanoma regardless of age, provided that PS is adequate [5]. In clinical trials, patients with an ECOG score of 0 or 1 (KPS 80–100) were routinely enrolled, whereas in real-world data, patients with an ECOG score of 2 (KPS ≥70) were also included. However, an ECOG score of 3 or 4 (KPS <50) was a contraindication due to high toxicity risk [4, 6, 12]. Additionally, long-term follow-up confirms the durability of response to adjuvant nivolumab, which justifies treatment even in individuals in their ninth decade of life [13].

The next clinical challenge in our patient was the presence of severe aortic stenosis (AVA 0.7 cm^2, mean AV gradient 70 mmHg). AV disease was additional risk factors that required close monitoring. Cardio-oncology guidelines classify ICIs as cardiotoxic drugs and recommend a baseline cardiac evaluation, including ECG, echocardiography and troponin measurement prior to initiating

therapy [7]. In the case described, a monitoring protocol was implemented, including clinical assessment, ECG and troponin level testing before each nivolumab course. According to real-world data, ICI-triggered cardiotoxicity is rare, however it may occur several times more frequently than in registered studies. A monitoring protocol tailored to the patient's comorbidities ensures the earliest possible detection of the complications [8].

Demonstrating that adjuvant therapy can be safely and effectively administered in an 88-year-old patient with high cardiovascular risk including a significant AV stenosis significantly pushes the edges of what is traditionally considered too risky in oncology. The therapeutic success in this case confirms that a model of close multidisciplinary collaboration can fill the scientific evidence gap left by the strict criteria of clinical trials, ensuring patient safety for those with critical heart diseases. A limitation of this study is observation period, which is relatively short, and long-term cardiac safety requires further monitoring. As this is a single case report, generalizability is limited. Future multicenter studies should aim to include more octogenerian patients with significant comorbidities to build robust evidence for guideline development. Nevertheless, this case is a valuable example of an individualized therapeutic approach and effective multidisciplinary collaboration.

CONCLUSION

This case underscores the importance of integrating cardio-oncological assessment into routine practice for elderly melanoma patients, paving the way for broader inclusion criteria in future clinical trials. The described case highlights that advanced metrical age, even combined with severe cardiovascular risk, should not be a separate criterion for disqualification from adjuvant nivolumab immunotherapy of melanoma, which offers a realistic chance of preventing disease recurrence. The key factor for qualification should be functional status rather than chronological age. Customized cardio-oncological supervision, including monitoring of clinical status with vital signs, ECG, echocardiography and biomarkers allows for the safe administration of immunotherapy in patients with severe valvular heart disease. However, it is important to note the need for further clinical trials evaluating the safety and efficacy of immunotherapy in octogenarian and oldest old population.

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