Immune-related adverse events of immune checkpoint inhibitors and the impact of sex—what we know and what we need to learn

We read with interest the article by Khoja et al. [1], in which the authors reviewed systematically tumor- and class-specific patterns of immune-related adverse events of immune-checkpoint inhibitors. Their analysis revealed distinct immune related adverse events (irAE) profiles for anti-CTLA4 and anti-PD1/PDL1 antibodies, as well as different tumor histologies.

The authors correctly point out various factors which could contribute to these distinct irAE profiles in different tumor types, such as differences in the immune cell infiltration and neoantigen formation, and suggest that differences in patient characteristics, such as pharmacologic responses, microbiome and comorbidities may as well play a role in this context. However, they do not mention a further important determinant of immune responses: a patient’s sex.

Sex is a biological variable that affects immune responses to both self and foreign antigens across various species [2]. Different mechanisms could contribute to the overall stronger immune responses found in women as compared with men, including the localization of immune related genes and miRNA implicated in their regulation on the X chromosome and the control of immune cell differentiation and function by sex hormones [2]. The incidence of autoimmune diseases is significantly higher in women, and alterations of sex hormone levels in pregnancy or menopause are known to affect their outcome [2]. Thus, types, frequency and/or severity of irAEs may—in addition to the factors discussed by Khoja et al. —as well be influenced by sex.

While the sexual dimorphism in drug response, with differences in metabolism due to variances in body size, distribution volume, sex hormone levels and activity of enzymes may as well play a role in this context. However, they do not mention a further important determinant of immune responses: a patient’s sex.

Generally, in oncology, the balance between the efficacy and toxicity of a drug might not be the same in men and in women. To understand this balance is a major challenge for drug development. Especially for checkpoint inhibitors, and in view of a positive correlation between the occurrence of irAEs and response rates, the question whether sex differences are present is of particular importance [4]. There is emerging evidence from animal experiments showing that PD-1 expression is sex-dependent and modulated by estrogens. Moreover, data from preclinical melanoma models and clinical trials suggests that female sex is a predictor of poor response to anti-PD-1 therapy [5]. To the best of our knowledge, data on the impact of sex on tumor response, as well as a possible correlation with irAEs for different types of checkpoint inhibitors and tumor types have not been reported and are urgently required. Inadequate inclusion of women in clinical trials in many disciplines, including oncology, despite the recommendations of important regulatory bodies such as the Food and Drug Administration and the National Institute of Health [6] is only one reason why obtaining this kind of data is challenging.

In our view, sex is a fundamental biological variable, affecting a vast range of cellular functions in different organs, with impact in both physiological and pathological conditions, which deserves more attention in oncology.

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References

PD-1 blockade with nivolumab in endemic Kaposi sarcoma

We report two cases of non-HIV associated Kaposi sarcoma (KS) patients who achieved major clinical and metabolic responses following the administration of the anti-programmed death 1 (PD-1) antibody nivolumab.

A 74-year-old patient (patient 1) and a 64-year-old patient (patient 2) were diagnosed with monomorphic endemic KS. The first patient initially presented with cutaneous involvement and subsequent muscular, bone and lymph node extension that were successively treated with radiation therapy, bleomycin, vincristine, anthracyclines and paclitaxel; the second patient had bone and lymph node extension, previously treated with radiation.
therapy, and anthracyclines. Little and non-durable benefit were observed in both cases. In 2016, severe disease progression was diagnosed, requiring the daily use of opioids and resulting in severe walking disability (patients 1 and 2) and complicated with Staphylococcus aureus than Proteus mirabilis osteomyelitis of the right ankle (patient 2). Both refused amputation. Considering the well-known immunomodulation of KS, the major efficacy of anti-PD-1 antibody in Merkel cell carcinoma [1], another virus-associated immunomodulated tumor, and since no other standard therapy was available, they received nivolumab 3 mg/kg every 2 weeks. Twelve weeks after starting nivolumab (six cycles), 18F-2-fluoro-2-deoxy-D-glucose positon emission tomography (FDG-PET) showed significant partial response for both patients. The walking function of patients 1 and 2 improved and opioids were stopped. After 24 weeks (12 cycles of nivolumab), the clinical benefit was confirmed (Figure 1). Last tumor evaluation (FDG-PET and magnetic resonance imaging) showed stable partial response for both patients except for one preexisting nodule on the right foot, which required concomitant radiotherapy (patient 1). In patient 2, the P. mirabilis osteomyelitis was treated with ceftriaxone for 6 months and was stable. Tumor biopsies carried out at baseline were retrospectively tested for PD-L1 expression using immunohistochemistry. PD-L1 was positive in patient 1 (1%–5% of tumor cells) and negative in patient 2 (<1%). Clinical tolerance was good; a biological adrenal insufficiency revealed by hyponatremia associated with a low cortisol and a normal adrenocorticotropic hormone (ACTH) level was diagnosed after 16 weeks (patient 1), requiring hormone-replacement therapy.

Classic and endemic KS is a cutaneous lymphangioproliferation associated with human herpes virus 8, occurring in patients without HIV infection nor iatrogenic immunosuppression. Treatment is based on chemotherapy, mainly anthracycline or paclitaxel resulting in 30%–60% of transient responses, or interferon therapy which is poorly tolerated [2, 3]. Immunotherapy has proven to be effective in several solid cancers including Merkel cell carcinoma [1]. Moreover, recent data demonstrated that PD-1 is expressed on tumor cells or in tumor microenvironment in KS [4] and that it inhibits NK cells functions, thus promoting tumor progression [5].

These two cases suggest that anti-PD-1 blockade with nivolumab could be effective in the treatment of refractory KS. Prospective clinical studies are warranted to confirm this result.

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Figure 1. 18F-fluorodeoxyglucose positon emission tomography (FDG-PET) response: maximum-intensity projection images from FDG-PET of the two patients at baseline and at 24 weeks. A and B, Patient 1 had a partial metabolic response after treatment with nivolumab, with complete regression of skin lesions (SUVmax = 2 versus 26.2), almost complete resolution of pathological hypermetabolism in inguinal lymph nodes (SUVmax = 4.7 versus 27.4), and partial regression of FDG uptake in foot bone lesions (SUVmax = 14.1 versus 23.7). C and D, Patient 2 had a partial metabolic response in most lymph nodes (right inguinal lymph nodes, SUVmax = 25.3 versus 27.4), intra-muscular and subcutaneous lesions (inner right thigh SUVmax = 18.4 versus 26.1). Only bone hypermetabolism related to osteomyelitis was not decreased on FDG-PET (SUVmax = 24.6 versus 23.7).
Recommendations for the clinical management of the elderly patient with malignant lymphoma

We write to express our concerns regarding the recent publication in the Annals of Oncology of recommendations for the clinical management of the elderly patient with malignant lymphoma from an ESMO Consensus Conference. In the past, ESMO has always supported a balanced and multidisciplinary approach to the treatment of malignant diseases, and we were therefore surprised and disappointed that these recommendations lacked a clear definition of the role for radiation therapy (RT) and expertise in this area in the authorship of the ‘multidisciplinary panel’ of 25 leading experts [1].

RT remains the most active single modality in the local treatment of most types of lymphoma and an important component of combined modality therapy in improving outcomes for patients. Modern limited and highly conformal RT to even low doses [2, 3] is highly effective and well tolerated by older patients, who often tolerate chemotherapy poorly and thus receive compromised regimens. Notably, the risk of radiation-induced second malignancies, which has largely driven the decreased use of RT, is not relevant in older patients as demonstrated in analyses of large databases. Intensive salvage therapy to frequently refractory and relapsed disease is often precluded in older patients, hence achievement of a durable remission with first-line combined modality treatment is even more crucial in older than in younger patients. Therefore, RT has a particularly important role to play in the often difficult management of lymphomas in older patients, and its omission from the published recommendations is of concern in maintaining the best outcomes for older patients with lymphomas.

For patients with localized disease, local RT is an important part of curative treatment, either alone for indolent lymphomas or in combination with brief systemic treatment for aggressive lymphomas. Localized disease is most common in diffuse large B-cell lymphomas (30%–40% of cases), and in these patients even RT alone may be curative, thus providing an attractive treatment option for patients too old or frail to tolerate chemotherapy. For patients with advanced aggressive lymphomas, RT to residual disease after chemotherapy or to bulky and extra-nodal sites may offer a chance to achieve a more favorable outcome. Finally, RT is an excellent palliative treatment for indolent lymphomas in older patients, where doses as low as 4 Gy in two fractions offer durable local control with minor if any side-effects.

These aspects of the treatment of lymphomas in older patients are seemingly absent in this ESMO paper in stark contrast to The International Society of Geriatric Oncology published guidelines for the use of RT for elderly patients, including patients with lymphoma [4], and to several recently published ESMO Guidelines on the management of different lymphomas. We hope that ESMO and Annals of Oncology will continue to support and ensure a balanced multidisciplinary approach to the treatment of malignant diseases, including lymphomas.

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