The interactions between antihypertensive drugs and novel anticancer therapy

Marijana Tadic\textsuperscript{a} and Guido Grassi\textsuperscript{b}

Anticancer therapy significantly developed over last 2 decades which significantly prolonged life of cancer patients, but also revealed new issue – a broad spectrum of toxicity reactions of which cardiotoxicity has the most important role in prognosis of cancer patients, aside to their primary disease. The revolution in anticancer therapy was achieved by immune checkpoint inhibitors (ICIs), which made a revolution in treatment of various hematologic and solid cancers (nonsmall-cell lung cancer, renal-cell carcinoma, melanoma, hepatocellular carcinoma, malignant pleural mesothelioma, colorectal cancer). Several ICIs have been developed to restore the T-cell-mediated immune response and improve the efficacy of antitumor treatments: inhibitors of the programmed cell death protein 1 (nivolumab and pembrolizumab), inhibitors of programmed cell death-ligand 1 (atezolizumab, avelumab and durvalumab), and inhibitors of cytotoxic T lymphocyte-associated antigen-4 (ipilimumab and tremelimumab). Immune-mediated toxicities may affect any organ or tissue including the skin, endocrine or gastrointestinal system, lung, liver or heart. The majority of these side effects can be controlled by glucocorticoid therapy \cite{1}. ICIs can be associated with myocardial damage (myocarditis, heart failure, infarction, Takotsubo syndrome), pericardial disease (pericarditis, effusion, tamponade), arrhythmias and vascular injury \cite{2}.

A SEER-medicare study included 5730 patients who received chemotherapy and 675 patients who received chemotherapy and ICIs \cite{3}. Findings showed that overall cardiovascular toxicity was significantly lower in ICIs-treated patients than in participants with chemotherapy. The risk for heart failure, cardiac arrhythmia and heart blocks was significantly lower among cancer patients treated with ICIs than those who received chemotherapy \cite{3}. There was no difference in acute coronary syndrome, cardiomyopathy, pericarditis and myocarditis between the two cohorts \cite{3}. Patients older than 75 years, with comorbidities and preexisting heart disease, were at higher risk for cardiovascular toxicity. These results show that the addition of ICI therapy to chemotherapy is safe and does not increase, but in fact decrease, cardiotoxicity in cancer patients \cite{3}.

Angiotensin-converting enzyme inhibitors (ACEI) and angiotensin-II receptor blockers (ARB) alone or in combination with beta-blockers are recommended for treatment of anticancer therapy-induced cardiac damage or for cardiac protection during anticancer treatment \cite{4}. However, effect of ACEI/ARB during ICI therapy is controversial because these agents may favor a proinflammatory state within the tumor, which induces an immunosuppressive milieu \cite{5}. Recently published animal study showed that captopril therapy moderates the immune response by infiltration and modification the phenotypical composition of T lymphocytes and may be an important additional mechanism for tumor control \cite{6}. Captopril significantly decreased tumor viability and slowed growth of colorectal liver metastases in mice. Therefore, the concomitant use of ACEI/ARB might enhance the therapeutic efficacy of ICI. Study that investigated the effect of concomitant ACEI and ICIs treatment showed worse outcome in patients with advanced nonsmall-cell lung cancer \cite{7}. This association was independent of typical prognostic factors. This underlined an immunosuppressive state in ACEI group.

In the current issue of the Journal, Kichenadasse \textit{et al.} \cite{8} reported that concomitant use of antihypertensive patients including ACEI and ARB was not related with survival and immune-related safety outcomes during ICI (atezolizumab) therapy for solid cancers. The authors included 3695 cancer patients from seven published trials of whom 2539 were treated with atezolizumab and the rest with chemotherapy. There was no difference in overall survival (OS), progression-free survival or immune adverse events between atezolizumab-managed patients who were not treated with antihypertensive medication or concomitantly treated with ACEI/ARB \cite{8}. Other classes of antihypertensive patients were also not related with survival. Potential confounding variables (age, sex, race, performance status, BMI, the number of sites of tumor metastases, comorbidities – diabetes, cardiovascular disease, hypertension and renal failure) were included in multivariable analysis. The
majority of patients who were treated with ACEI or ARB had arterial hypertension (95%), whereas renin–angiotensin–aldosterone system (RAAS) inhibitors were used for ischemic heart disease and congestive heart failure in less than 5% of all cancer patients treated with atezolizumab. The only potential antihypertensive drug class that was associated with worse OS in cancer patients treated with chemotherapy and not ICIs was diuretics [8].

Cortellini et al. [9] investigated the influence of concomitant medications in 1012 cancer patients (nonsmall-cell lung cancer, renal-cell carcinoma and melanoma) treated with ICIs. The authors demonstrated that ACEI/ARB, beta-blockers or calcium channel blockers were not associated with progression-free survival or OS neither in univariable nor in multivariable analysis [9]. It was also reported that the concomitant treatment with ACEI/ARB was not associated with performance status and burden of disease calculated by number of metastatic sites in ICIs-treated cancer patients. The same was reported for calcium channel blockers, whereas beta-blockers were more frequently prescribed in patients with more than two metastatic sites [9]. These findings are in line with the results of the current study that also did not reveal any association between RAAS inhibitors and outcome in ICIs-treated patients.

Study from the Mayo Clinic also included large number (n = 3326) of patients treated with ICIs (atezolizumab, avelumab, ipilimumab, nivolumab and pembrolizumab) and found that therapy with ACEI/ARB, statins and ezetimibe was also not associated with increased all-cause mortality cancer patients treated with ICIs [10]. Prior beta-blocker use, but not therapy with other antihypertensive patients including RAAS inhibitors, was associated with increased mortality only in patients with lung cancer. This is important finding considering the fact that 44% study participants were treated with RAAS inhibitors and 54% patients were treated with beta-blockers, which represents a representative cohort of patients and makes this study valid for drawing conclusions.

Medjebar et al. [7] included 178 patients with nonsmall-cell lung cancer of whom only 22 patients received ACEI and found that ACEI-treated patients significantly shorter median progression-free survival in comparison with the control group, which raised the question about potential association between ACEI and adverse outcome in ICIs-treated cancer patients. The multivariable analysis that included the main clinical characteristics reported significant association between ACEI therapy and OS, as well as progression-free survival, in ICIs-treated cancer patients [7]. RNA sequencing suggested that tumors from the ACEI group had less macrophages, activated mast cells, natural killer cells and memory-activated T cells, which implied an immunosuppressed condition. However, this study included a very limited number of patients and particularly ACEI-treated participants and therefore conclusion has a limited value [7]. Furthermore, the authors investigated only the effect of captopril, which is rarely used in everyday clinical practice and represents an additional important limitation of this study.

In the current study, authors reported significant difference in prevalence of hypertension, cardiovascular diseases, diabetes and renal failure between patients who were treated and those who were not treated with RAAS inhibitors [8]. The use of other antihypertensive patients (calcium channel blocker, beta-blockers and diuretics) was also more prevalent among patients who were treated with RAAS inhibitors, which is associated with hypertension and other cardiovascular diseases. Concomitant use of several antihypertensive patients was inevitable and therefore it is challenging to separate the effect of RAAS inhibitors from other antihypertensive patients, despite multivariable analysis that is mainly used for this purpose. Atezolizumab was the only ICI used in this study, which represents additional limitation of this study. Furthermore, different RAAS inhibitors in various dosages were used in seven trials that were included in this study, which also can impact the final results. During trials that investigated effect of ICIs some antihypertensive medications were initiated, whereas others were discontinued. One should also emphasize that duration of RAAS inhibitors therapy was not considered in this study, which also might have an important influence on the association between RAAS inhibitors, ICIs and outcome because chronic ACEI and ARB use has important and independent protective effect on cardiovascular remodeling and outcome in hypertensive patients. This may have an important effect on final results, which is difficult to control in study that combined results from seven trials.

ICIs made revolution in anticancer therapy in some of the most challenging cancers such as nonsmall-cell lung cancer, renal-cell carcinoma and melanoma. Current investigation included 3695 patients from seven clinical trials of lung, renal or urothelial cancers who were treated with atezolizumab. The concurrent treatment with RAAS inhibitors or other antihypertensive classes was not associated with OS, progression-free survival and immune-related adverse events from cancer immunotherapy drug, atezolizumab. Previous preclinical and some clinical data indicated potential synergetic effect of RAAS inhibitors and ICIs in cancer patients, whereas other investigations reported negative relationship between these two groups of drugs and outcome in these patients. Further longitudinal studies with a large number of cancer patients with various cancer types treated with different ICI drugs and concomitant RAAS inhibitors are warranted to explain a complex relationship between cancer, anticancer and antihypertensive therapies.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES


