

Cardiovascular risk profile and events before and after treatment with anti-VEGF drugs in the setting of a structured cardio-oncologic program

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Online publish-ahead-of-print 7 May 2020

Drugs targeting the vascular endothelial growth factor (VEGF) pathway represent a successful therapeutic option for several solid malignancies, but are burdened by the risk of developing cardiovascular (CV) and renal adverse events (CVAEs).¹ Arterial hypertension, proteinuria and impairment of renal function are the most common AEs due to anti-VEGF drugs.² For many anticancer therapies, the risk of developing CVAEs is related to the baseline CV risk profile,³ and traditional CV risk factors have, indeed, been shown to predict CVAEs also in subjects receiving anti-VEGF agents.² Nevertheless, data regarding the prevalence of CV risk factors among oncologic patients are scarce.⁴ Moreover, in the oncologic setting, CV risk factors are typically defined only on the basis of clinical history (i.e. present/absent), and information regarding their control is frequently missing. Yet, the predisposition that a given CV risk factor confers towards CVAEs due to anticancer therapies is expected to be stronger if it is uncontrolled or untreated; on the other hand, the association may be blunted if it is well controlled.⁵

Despite CVAEs due to anti-VEGF agents being well described, there is a lack of real-world data regarding the CV risk profile and the rate of CVAEs in patients receiving anti-VEGF treatments, especially when regular cardio-oncologic consultation is provided.

In this retrospective study, we reviewed the records of all patients consecutively evaluated before starting an anti-VEGF therapy at the Cardio-Oncology Outpatient Clinic of the San Martino Polyclinic Hospital, University of Genova, Italy, from December 2015 to

December 2018. No exclusion criteria were applied. As per our practice, these patients received detailed education regarding the management of their CV profile and, in particular, the risk of increasing blood pressure (BP) values, including advice on when and with which drugs to manage new-onset or worsening hypertension.² Cardiologic recommendations were also communicated to the referring oncologists. After extracting the information about the baseline characteristics, we assessed the following outcomes at follow-up: a combined CV-renal endpoint, defined by medical re-evaluation due to uncontrolled arterial hypertension, worsening renal function (WRF; rise in serum creatinine ≥ 0.3 mg/dL from baseline values) and/or proteinuria (≥ 1 g/24 hours); major CV events; death; and discontinuation of anti-VEGF therapy. The last oncologic or cardio-oncologic evaluation, in which the patient was still undergoing anti-VEGF therapy, was considered as the last follow-up.

The study population included 85 patients, with a similar proportion of males and females and a mean age of 66 ± 10 years (Table 1). Forty-five (52.9%) patients had arterial hypertension, 45 (52.9%) were smokers (29 former and 16 current), 41 (48.9%) had dyslipidaemia, 16 (18.8%) had chronic kidney disease (CKD) and 11 (12.9%) had diabetes mellitus. In a significant number of cases, CV risk factors were not adequately controlled: 26.7% of the hypertensive patients had BP values not reaching the recommended goals^{6,7} and were given indications to optimize anti-hypertensive therapy; 56.8% of those with dyslipidaemia had serum lipid values not on target⁸ and/or were

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Table 1 Baseline characteristics of the study cohort.

	n = 85
Males	42 (49.4%)
Age (years)	66 ± 10
Type of malignancy	
Colon-rectal	26 (30.6%)
Kidney	22 (25.9%)
Breast	14 (16.5%)
Ovarian	11 (12.9%)
Other*	12 (14.1%)
Stage IV cancer	66 (77.7%)
Anti-VEGF drug	
Bevacizumab	54 (63.5%)
Pazopanib	11 (12.9%)
Sunitinib	10 (11.8%)
Sorafenib	5 (5.9%)
Other**	5 (5.9%)
Concurrent oncologic therapy (combined)	44 (51.8%)
Taxanes ^o	23 (27.1%)
Platinum	22 (25.9%)
Capecitabine ^{oo}	20 (23.5%)
Anthracyclines	2 (2.3%)
Previous exposition to anthracyclines	13 (15.3%)
Cardiovascular risk factors	
Arterial hypertension	45 (52.9%)
Dyslipidaemia	41 (48.2%)
Smoking	45 (52.9%)
Diabetes mellitus	11 (12.9%)
Family history of CAD	6 (7.1%)
≥2 risk factors	47 (55.3%)
Chronic kidney disease	16 (18.8%)
Prior CAD	4 (4.7%)
Peripheral artery disease	4 (4.7%)
Known heart failure	2 (2.4%)

VEGF: vascular endothelial growth factor; CAD: coronary artery disease.

*Includes hepatic cancer (3), thyroid cancer (2), sarcomas (2), chronic myeloid leukaemia (2), lung cancer (1), gastrointestinal stromal tumour (1) and cervical cancer (1).

**Includes cabozantinib (2), ponatinib (2) and lenvatinib (1).

^oIn 11 (12.9% of the overall cohort) cases as part of a platinum-based chemotherapy regimen, and in one case with anthracyclines.

^{oo}In 11 (12.9% of the overall cohort) cases as part of platinum-based chemotherapy.

not treated. At baseline evaluation, mean systolic BP was 131.7 ± 16.7 mmHg, mean diastolic BP 77.1 ± 9.8 mmHg and mean creatinine 1.0 ± 0.4 mg/dL.

Follow-up data were available for 67 patients. The median duration of follow-up was 233 (122–364) days. At the last evaluation, mean systolic BP was 135.1 ± 25.3 mmHg, mean diastolic BP 79.5 ± 10.2 mmHg and mean creatinine 1.1 ± 0.9 mg/dL, all of which were not significantly different from baseline ($p=0.49$, $p=0.36$ and $p=0.43$, respectively). The combined CV-renal endpoint occurred in 17 (25.4%) patients: seven (10.4%) needed an evaluation due to uncontrolled arterial hypertension, five (7.5%) developed WRF and six

(9.0%) proteinuria. Three (4.5%) patients experienced a major CV event: one had a pulmonary embolism, one an episode of heart failure during a respiratory tract infection and one a transient ischemic attack. The latter one was also evaluated for uncontrolled hypertension. Six (9.0%) patients died, all because of cancer progression. In 16 (23.9%) cases anti-VEGF treatment was stopped, but only in one subject due to a CV event (pulmonary embolism), and never because of uncontrolled hypertension. Baseline oncologic and CV characteristics of patients with and without the combined CV-renal endpoint were similar. In particular, arterial hypertension, uncontrolled arterial hypertension and CKD were no more frequent in those experiencing the combined endpoint ($p=0.18$, $p=0.14$ and $p=0.24$, respectively); nor were these conditions associated with the combined CV-renal endpoint at univariate regression, although the analysis was limited by the small numbers (arterial hypertension: odds ratio (OR) 2.04, 95% confidence interval (CI) 0.63–6.67, $p=0.24$; uncontrolled arterial hypertension: OR 2.56, 95% CI 0.67–9.52, $p=0.16$; CKD: OR 0.42, 95% CI 0.08–2.12, $p=0.29$).

In this real-world cohort of oncologic patients scheduled to receive anti-VEGF therapies, the prevalence of CV risk factors was substantial. Moreover, CV risk factors were not controlled in a significant proportion of subjects. The cardio-oncologic baseline evaluation was instrumental to adequately assess patients' CV profiles, adjust CV medications and recommend strategies to manage BP increases. Nonetheless, the incidence of the combined CV-renal endpoint was not trivial, with hypertension requiring medical attention occurring in about one in 10 patients. This finding indicates that some degree of vascular and renal dysfunction is hardly avoidable with anti-VEGF drugs. Notably, however, two of the seven patients requiring re-evaluation due to uncontrolled hypertension self-reported non-compliance with the recommended anti-hypertensive therapy. On the other hand, there were only three major CV events in our cohort, none of which were fatal and only one led to discontinuation of therapy. This is remarkable since the clinical relevance of vascular toxicities of anti-VEGF agents resides in treatment interruption and in the occurrence of major CV events.^{3,9}

Some shortcomings of our study should be acknowledged. The sample size was small and no control group was present; moreover, we focused on arterial hypertension, and data concerning the control of other CV risk factors (i.e. diabetes) were limited.

In conclusion, in subjects scheduled to receive anti-VEGF therapy, a cardio-oncologic baseline evaluation allowed for the adequate assessment of patients' CV profiles and adjustment for CV therapies. This approach resulted in a safe delivery of anticancer therapy. Our results confirm the importance of the cardio-oncologic visit for CV prevention and, in general, a holistic approach to minimize CV toxicity in the oncologic setting.¹⁰

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

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