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Review Article

Everolimus as cancer therapy: Cardiotoxic or an unexpected antiatherogenic agent? A narrative review

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ABSTRACT

Everolimus (EVE) is now approved by many agencies for the treatment of variable neoplasms. The risk for adverse events with this agent is not adequately defined. The purpose of this review is to summarize the EVE-induced cardiotoxic effect as an antineoplastic factor on patients who received the specific drug and to evaluate any possible antiatherogenic effects due to systemic use of the drug. Articles were searched on PubMed until August 2017. Articles included an expanded-access clinical trial, as well as phase 2 or 3 clinical trials (most of them were randomized). Three experimental studies that provided evidence for the possible antiatherogenic action of EVE were also included. In addition, only studies that evaluated the systemic use of the drug were included. To be eligible for inclusion, trials should have evaluated patients with malignancy, treated by EVE, or assessed the antiatherogenic effect of the systemic use of EVE through clinical or experimental studies. Only articles written in English language were included. No direct cardiotoxic adverse effects (arrhythmia, acute coronary event, heart failure, and echocardiography pathologic findings) were reported. Patients appeared to have a risk of developing adverse events that could be associated with the risk factors of cardiovascular disease. In all clinical studies, patients suffered hyperglycemia, and in most of them, hyperlipidemia was observed. Fewer studies have reported the incidence of hypertension. Finally, there is evidence claiming that EVE has an antiatherogenic action. Three experimental studies have shown that the systemic use of EVE in mice or rabbits with atherosclerotic lesions led to the reduction in atheromatous plaque growth. However, we could not find any clinical study that showed similar results in patients with cancer. To sum up, the only reported cardiac adverse event of EVE treatment in patients with cancer is indirect. They are associated with the risk factors of cardiovascular disease (hyperglycemia, hyperlipidemia, and hypertension), which are mainly mild and easily manageable. Further research and data that support the antiatherogenic action of EVE are needed.

1. Introduction

The use of new chemotherapeutic agents, during the past decades, has improved survival and the quality of life among patients with cancer. However, the applicability of these drugs is restricted by the risk of cardiotoxicity. Cardiotoxicity is one of the most important adverse reactions of chemotherapy and can appear earlier or later in the course of the disease.[5,6] As a result, patients should be closely monitored and followed for the early detection of any cardiac dysfunction.[7,8]

Everolimus (EVE; RAD001) has been, recently, developed as an antineoplastic factor against various types of cancer. This agent has been approved in oncology against advanced pancreatic neuroendocrine tumors (p-NETs), advanced renal cell carcinoma (RCC), and advanced hormone receptor-positive breast cancer in combination with exemestane and subependymal giant cell astrocytomas (SEGAs) associated with tuberous sclerosis.[9–12] EVE is a mammalian target of rapamycin (mTOR) inhibitor. The mammalian target of rapamycin (mTOR), a serine–threonine protein kinase, mediates cellular growth, proliferation, differentiation, and angiogenesis through multiple pathways.[1] It exists in two complexes, mTORC1 and mTORC2. EVE has an effect, solely, on the mTORC1 protein complex. It binds and forms a complex with intracellular FKBP-12, thus inhibiting the mTORC1 complex and phosphorylating P70

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ribosomal S6 protein kinase. In addition, EVE reduces the elongation factor 4E-BP1 (which is involved in protein synthesis), inhibits the expression of HIF-1, and controls angiogenic pathways through hypoxia-inducible factor 1a and VEGF, as well as through endothelial and smooth muscle cell proliferation.[2,3] Owing to its immunosuppressive action, the drug was, first, used as an immunosuppressive agent for prevention of acute rejection following solid organ transplantation.[4] In cardiology, EVE is available as a drug-coated stent and is used in percutaneous coronary interventions for prevention of restenosis. With its potent suppression of reactive neointimal ingrowth, this drug has been shown to significantly reduce in-stent neointimal hyperplasia.[13]

As with any other chemotherapeutic agent, EVE has its toxicity profile. The main adverse effects that have been reported in >10% of patients in phase II/III studies of EVE (compared to placebo) are stomatitis, rash, hyperglycemia, hyperlipidemia, fatigue, myelosuppression, and noninfectious pneumonitis.[10,14,21] Further evaluation of the cardiotoxic effects and drug interactions associated with EVE is required.

The aim of this review is to assess the cardiac toxicity of the drug and the adverse events (AEs) that correlate with the classical risk factors for coronary artery disease (CAD; mainly dyslipidemia, hyperglycemia, and hypertension), when administered to patients with cancer. In addition, we will summarize current evidence that supports the idea of EVE being used to target the whole pathogenesis of atherosclerosis and associate it, if possible, with patients with cancer.

2. Methods

Articles eligible for inclusion were identified by searching the PubMed database for a period up to August 2017. The terms/words that were used for the search were as follows: Everolimus AND arrhythmias OR heart failure OR ejection fraction OR electrocardiogram OR atheromatosis OR echocardiography OR hypertension OR hyperglycemia OR hyperlipidemia OR anti-atherogenic action. From 387 articles that resulted from the above search, only 36 were included to construct the review article. Thirteen of the included articles were studies on EVE: randomized phase II trials (1), randomized phase III trials (5), nonrandomized phase II trials (5), nonrandomized phase III trials (1), and an expanded access—clinical trial program. In addition, 3 experimental studies were also included. To be eligible for inclusion, the trials should have evaluated patients with malignancy, treated by EVE (not in combination with other chemotherapeutic agents), or assessed the antiatherogenic effect of the systemic use of EVE through clinical or experimental studies. We included only articles written in English. The majority of the other studies were excluded with regard to (local delivery) EVE-eluting stents (218) and EVE immunosuppressive therapy in patients with renal or heart transplant (105). In addition, 22 articles were excluded as case reports (non—statistically significant result) and 6 as articles in non—English language. AEs were defined as per the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) versions 2.0 and 3.0. Sample size, number of all grades and types of cardiac AEs, and patients' characteristics were recorded.

3. Results

3.1. Everolimus and direct cardiotoxicity

The use of EVE has a direct cardiotoxic effect and could be associated with acute coronary events, arrhythmias, symptoms or signs associated with acute heart failure, clinically important deterioration of left ventricle ejection fraction (defined as a decrease in LVEF at least 10% between the baseline and follow-up echocardiography study), and pericardial reaction. On searching the available database, we did not find any trial or study report of patients with cancer, treated with EVE, to be associated with these adverse effects.

3.2. Everolimus and risk factors for CAD

The classical modifiable risk factors for CAD are hypercholesterolemia (especially high blood levels of LDL), hypertension, diabetes mellitus, cigarette smoking, absence of physical activity, obesity, and metabolic syndrome. There have been many trials that have reported the incidence of hyperglycemia, hypercholesterolemia, and hypertriglyceridemia in patients receiving EVE as cancer therapy. Fewer studies support the incidence of hypertension in the same category of patients. This is due to the drug's adverse effects that can be associated with a possible triggering of cardiovascular events (Table 1).

We present 13 studies that have evaluated the use of EVE in patients with cancer. In all of them, hyperglycemia presented as a side effect. Additionally, in 9 of 13 studies, patients presented dyslipidemia as a side effect, and only in 2 studies, hypertension appeared as an adverse effect. In most of the cases, AEs were Grade 1 or 2.

In REACT (an expanded-access clinical trial), 1367 patients who received EVE against VEGF-refractory metastatic RCC (mRCC) were studied. Of these patients, 6% developed hyperglycemia (only 4% of this group discontinued the drug) and 1% developed hypercholesterolemia (only 7% of this group discontinued the drug).[17]

In RECORD-1 (phase III trial), 277 patients with mRCC were given EVE versus 139 patients on placebo. Of them, 12% of patients treated with EVE developed hyperglycemia and 20% developed hypercholesterolemia. The median time for developing these side effects was 4.3 weeks from the start of the drug, and no patients needed to discontinue treatment. The incidence of these events was markedly higher in the EVE group than the placebo one.[18]

Choueiri et al evaluated EVE versus cabozantinib in patients with advanced RCC and a clear histology (METEOR, a randomized open-label phase III study). In this study, 19% of patients who received EVE were reported with hyperglycemia and 13% with hypertriglyceridemia. These specific adverse effects were markedly higher in the EVE treatment group versus the cabozantinib treatment group. Dose modifications were effective in minimizing or preventing treatment-associated discontinuations. A small amount (8%) of patients who received EVE suffered with hypertension.[15]

In 2011, *Pavel et al* evaluated 246 patients with biopsy-proven unresectable or metastatic NET and treated with EVE in an open-label, multicenter, phase IIIb, expanded-access study. Of them, 12.2% of patients with pancreatic NET (p-NET) appeared to be hyperglycemic after EVE treatment, while 5.1% of patients in the non-p-NET group suffered the same adverse effect. In addition, 4.1% of patients with p-NET and 5.1% of them with non-p-NET were found to have hypertension after the therapy.[16]

Armstrong et al evaluated EVE versus sunitinib in patients with metastatic non—clear cell renal carcinoma in a multicenter, open-label, randomized, phase II trial (ASPEN). From 57 patients who received EVE, 12% developed hyperglycemia and 14% developed hypercholesterolemia.[17]

Yao et al enrolled patients with advanced, progressive, well-differentiated, nonfunctional neuroendocrine tumors of lung or gastrointestinal origin in a randomized double-blind, placebo-controlled phase III trial (RADIANT-4). From 205 patients who received EVE, 10% appeared to develop hyperglycemia. No other adverse effects associated with risk factors of CAD were noticed.[20]

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Table 1
Studies and results of everolimus adverse events that are associated with the risk factors for CAD.

Study/Trial	Type	Subject	No. of patients (Treated with eve)	Everolimus AEs associated with the risk factors of CAD		
				AE1: Hyperglycemia	AE2: Dyslipidemia	AE3: Hypertension
REACT[15]	Expanded-Access Clinical Trial program	Everolimus against VEGF- refractory mRCC	1367	GRADE 1–2: 0.3% GRADE 3: 5.1% GRADE 4: 0.6%	GRADE 1–2: 0.2% GRADE 3: 0.7% GRADE 4: 0.2%	–
RECORD-1[16]	Phase III, randomized, double-blind trial	EVE treatment in patients with mRCC which had progressed on sunitinib, sorafenib, or both	272	GRADE 1–2: 5.7% GRADE 3: 6.3% GRADE 4: 0%	GRADE 1–2: 16.8% GRADE 3: 3.2% GRADE 4: 0%	–
METEOR[13]	Open-label, randomized, phase III trial	Cabozantinib versus EVE in advanced renal cell carcinoma	328	GRADE 1–2: 14% GRADE 3: 5% GRADE 4: 0%	HTG GRADE 1–2: 10% GRADE 3: 2% GRADE 4: 1%	GRADE 1–2: 4% GRADE 3: 4% GRADE 4: 0%
ASPEN[17]	Multicenter, open-label, randomized phase II trial	EVE versus sunitinib in patients with metastatic non–clear cell renal carcinoma	57	GRADE 1–2: 12% GRADE 3: 0% GRADE 4: 0%	HTG GRADE 1–2: 9% GRADE 3: 5% GRADE 4: 0%	–
Pavel et al.[14] (2011-2012)	Open-label, multicenter, phase IIIb expanded-access study	EVE treatment in patients with biopsy-proven, unresectable or metastatic NET	246 126 with p-NET, 120 with non-p-NET	GRADE 1–2: 5.7% p-NET, 1.7% non-p-NET GRADE 3: 6.5% p-NET, 3.4% non-p-NET GRADE 4: 0%	–	GRADE 1–2: 2.5% p-NET, 2.4% non-p-NET GRADE 3: 1.6% p-NET, 1.7% non-p-NET GRADE 4: 0%
RADIANT-3[24]	Prospective, randomized, phase III study	Patients with advanced, progressive, low- or intermediate-grade pancreatic NET were randomly assigned to EVE or placebo	207	GRADE 1–2: 8% GRADE 3–4: 5%	–	–
RADIANT-4[18]	Randomized, double-blind, phase III trial	EVE versus placebo in patients with advanced, progressive, well-differentiated, nonfunctional NETs of lung or gastrointestinal origin	205	GRADE 1–2: 7% GRADE 3: 3% GRADE 4: 0%	–	–
BOLERO-2[19]	International, multicenter, double-blind study	Combination of EVE and exemestane vs placebo and exemestane in a patient population of postmenopausal, hormone receptor–positive, advanced breast cancer	482	GRADE 1–2: 10% GRADE 3–4: 6%	GRADE 1–2: 13% GRADE 3–4: 1%	–
Yoo et al.[20]	Multicenter phase II trial	EVE treatment in patients with histologically confirmed metastatic or recurrent, unresectable bone and soft tissue sarcomas (except GIST, chondrosarcoma, and neuroblastoma)	41	GRADE 1: 61% GRADE 2: 10% GRADE 3: 12% GRADE 4: 2%	HTG GRADE 1: 32% GRADE 2-3-4: 0%	–
Oh et al.[22]	Multicenter, single-arm, open-label phase II study	EVE treatment in patients with histologically or cytologically confirmed nonfunctioning NETs	34	GRADE 1–2: 5.9% GRADE 3–4: 5.9%	–	–
Yoon et al.[23]	Prospective, open-label, single-arm phase II study	EVE treatment in patients with advanced, unresectable, and histologically confirmed adenocarcinomas of the stomach	54	GRADE 1–2: 66.7% GRADE 3–4: 20.4%	GRADE 1–2: 44% HCL, 24.1% HTG GRADE 3–4: 0%	–
Armato et al.[25]	2-stage, single-arm, phase II trial	EVE treatment in patients with mRCC	41	GRADE 1: 41% GRADE 2: 10.3% GRADE 3: 7.7% GRADE 4: 0%	GRADE 1: 25.6% GRADE 2: 25.6% GRADE 3: 5.1% GRADE 4: 0%	–
Wolpin et al.[9]	Multi-institutional, single-arm, phase II study	EVE treatment in patients with gemcitabine-refractory, metastatic pancreatic cancer	31	GRADE 1–2: 48% GRADE 3: 18% GRADE 4: 0%	GRADE 1–2: 18% GRADE 3: 3% GRADE 4: 0%	–

Abbreviations: mRCC = metastatic renal cell carcinoma; p-NET = pancreatic neuroendrocrine tumor; HTG = Hypertriglyceridemia; HCL = Hypercholesterolemia; EVE = Everolimus.

Previously, in another prospective, randomized phase III study (RADIANT-3), they evaluated 207 patients with low-grade or intermediate-grade advanced (unresectable or metastatic) p-NET. Of the 207 patients, 13% of them suffered hyperglycemia as an adverse effect.[9]

Rugo et al reported a group of postmenopausal women with hormone receptor–positive advanced breast cancer, who participated in an international, multicenter, double-blind study (BOLERO-2). Four hundred eighty-two patients were treated with EVE and exemestane, while 238 patients received placebo and exemestane. In the first group, 16% of patients developed the adverse effect of hyperglycemia and 14% developed hyperlipidemia (the incidence was markedly higher than that in the second group). Half of AEs occurred within the first 6 weeks of treatment. Nearly a half of the patients who received EVE and developed grade 3 or 4 hyperglycemia and hyperlipidemia experienced resolution to grade $\leq$1 after a median of 29.1 weeks. Only 0.2% of patients with hyperglycemia discontinued the drug.[21]

Yoo et al enrolled 41 patients with histologically confirmed metastatic or recurrent unresectable bone and soft tissue sarcomas (except GIST, chondrosarcoma, and neuroblastoma) in a multicenter phase II trial. Forty-one patients received EVE, 85% of whom developed hyperglycemia and 32% developed hypertriglyceridemia. These adverse effects were generally mild.[22]

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Milowski et al evaluated 45 patients with previously treated progressive metastatic urothelial carcinoma of the bladder, renal pelvis, ureter, or urethra (histologically confirmed) in a single-arm, nonrandomized study. In this study, 93% of patients suffered with hyperglycemia, 64% with hypercholesterolemia, and 62% with hypertriglyceridemia.[23]

Oh et al proceeded to a multicenter, single-arm, open-label phase II study in which 34 patients with histologically or cytologically confirmed nonfunctioning NETs were evaluated. A total of 34 patients were studied. Hyperglycemia was one of the main adverse effects of the drug (appeared in 11.8% of patients).[24]

Yoon et al enrolled 54 patients to perform a prospective, open-label, single-arm phase II study. Patients with advanced, unresectable, and histologically confirmed adenocarcinomas of the stomach were eligible. The prevalence of hypercholesterolemia was 44.4%, of hypertriglyceridemia was 24.1%, and of hyperglycemia was 87%.[25]

Amato et al evaluated 41 patients with clear cell Mrcc, who were receiving daily treatment (EVE) in a 2-stage, single-arm, phase II trial. The major AEs were hyperglycemia (59%), hypercholesterolemia (43.6%), and hypertriglyceridemia (56.3%).[25]

Wolpin et al performed a multi-institutional, single-arm, phase II study in 31 patients treated with EVE for gemcitabine-refractory metastatic pancreatic cancer. Hyperglycemia was observed in 66% of the patients, while hypercholesterolemia was observed in 21% of them.[26]

3.3. *Everolimus and antiatherogenic action*

The studies that have occurred until now and have supported a clear relationship between EVE and the antiatherogenic action consist of animal groups (mice and rabbits). We came up with 3 experimental studies, which are mentioned below.

In 2007, Mueller et al evaluated the subcutaneous use of EVE in LDL receptor−deficient mice fed with a diet rich in cholesterol. After the use of EVE, the atherosclerotic lesions in mice arteries were reduced by 44%−85%.[27]

Some years later, Beutner et al assessed, again, the effect of (per os) EVE on pre-existing atherosclerosis in LDL receptor−deficient mice. Atherosclerotic lesions were reduced up to 40%. In both studies, VLDL and LDL were increased after the use of the drug.[28]

Baetta et al evaluated the (per os) use of EVE in cholesterol-fed rabbits. They found that existing atherosclerotic lesions reduced up to 38%.[29]

Concerning clinical studies, EVE is also used in drug-eluting stents (topically) for patients with acute coronary events, a fact that supports the association between EVE and antiatherogenic action. We decided not to use the results of such studies in our review, as they did not refer to the systematic use of the drug.

4. Discussion

EVE was, initially, approved as an anticancer agent from Food and Drug Administration (FDA) in 2009 [particularly for adults with advanced RCC after failure of treatment with sunitinib or sorafenib]. Since then, the drug has also been used against other types of cancer, something that urged researchers to study its efficacy and safety. In this review, we tried to focus on the possible cardiac toxicity or AEs of EVE. First, we searched for any literature that could associate the drug's use with a direct cardiac side effect, especially an arrhythmia, an acute coronary event, a toxic effect to the heart's myocardium leading to heart failure or even any recorded incidents of pericardial infusion. Luckily for the patients, there were not any notable AEs associated with direct cardiotoxicity in most of the studies.

In addition, we thought that it was important to evaluate the effect of EVE on factors that are thought to be classical modifiable risk factors of CAD. It should be noted that CAD is considered as the most common type of cardiovascular disease worldwide. It appeared that EVE use caused three types of AEs that could be associated with the risk factors such as hyperglycemia, hyperlipidemia, and hypertension.

Hyperglycemia presented to all studies, we came up with, during the research. The mTOR pathway is highly associated with the insulin signaling pathway. As a consequence, mTOR inhibitors can worsen insulin metabolism, multiply insulin resistance, and weaken the activity of beta-cells. All these factors can cause hyperglycemia.[28,29] EVE may further impair glycemic control in patients who have increased baseline glucose levels. However, as we can see from Table 1, hyperglycemia was mild (most of them Grade 1−2) and easily manageable by antidiabetic agents. The need for dose reduction or drug discontinuation was rare.[15,18,21] Patients should be monitored for hyperglycemia, before and during EVE treatment, as poor glycemic control is associated with the development of microvascular disease.

Hyperlipidemia (hypercholesterolemia and hypertriglyceridemia) was the second most usual AE associated with increased risk for CAD. As we can see in Table 1, hyperlipidemia appeared as an AE in most of the available studies. It must be noted that there were not any reported measurements of LDL. mTOR inhibition leads to suppression of lipases activity. As a result, EVE lowers the catabolism of lipoproteins in the plasma and causes dyslipidemia.[30] In addition, EVE reduces the capacity of the adipose tissue for plasma lipid clearance. Nonetheless, the incidence of grade 3−4 hypercholesterolemia or hypertriglyceridemia was very low and dyslipidemia, in general, easily treatable. Again, patients should be observed for lipid disturbances before and during the treatment.

Finally, hypertension was reported only in 2 of 13 studies, as shown in Table 1, with most of cases being mild (Grade 1−2 AEs). There is not so clear association between the use of EVE and hypertension, as with the other two risk factors of CAD that we mentioned above.

On searching the available database for the association between EVE and atherosclerosis, we found experimental evidence indicating that EVE has pleiotropic antiatherosclerotic effects that can inhibit or detain the pathogenesis of atherosclerosis. These effects include blockade of smooth muscle cell migration and proliferation, impairment of monocyte chemotaxis, and the avoidance of lipid accumulation in macrophages and smooth muscle cells.[29,31–33]

Additionally, EVE induces basal autophagy by selectively promoting macrophage death in atherosclerotic plaques. As a result, the plaque cells can be protected against oxidative stress by degrading damaged intracellular material, in particular polarized mitochondria. In this way, successful autophagy of the damaged components promotes cell survival, without causing the deleterious effect of excessive autophagy (plaque destabilization because of the reduced synthesis of collagen and thinning of fibrous cap).[34] All these come into line with the experimental studies we mentioned above, in which the systematic use of EVE induced the reduction of atherosclerotic lesions. However, more studies must be performed to support this evidence.

5. Limitations

The main disadvantages of this specific review are its narrative character (as it is not a systematic one), the mediocre number of studies, and the lack of targeted clinical studies evaluating the direct effects (positive or negative ones) of EVE on the cardiovascular system of patients with cancer. We also included different

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studies (clinical and experimental ones) in our article and excluded reviews evaluating any local delivery effects of the drug. However, we managed to summarize the main adverse effects that could deregulate risk factors of CAD and that oncologists should be aware of. In addition, we refer to the pathophysiological effects of the use of EVE in patients with CAD, something that could be a trigger for new clinical studies to examine this specific correlation.

6. Conclusion

To sum up, EVE safety is satisfactorily evaluated in patients with cancer. There are nearly zero reports of the drug having a direct cardiotoxic effect on the patients. On the other hand, we can assume that the drug may deteriorate classical risk factors of cardiovascular disease (hyperglycemia, hyperlipidemia, and maybe hypertension). However, these AEs are of low to medium grade and are easily treatable. They should be monitored and managed. New evidence supports that the systematic use of EVE (and mTOR inhibitors, in general) could be a sidekick against atheromatosis because they stabilize and cease further development of atheromatic plaques. For patients with cancer, already on EVE treatment, the specific drug could have an “unexpected” cardioprotective property, as long as any AEs are efficiently treated.

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