Everolimus therapy and side-effects: A systematic review and meta-analysis

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Abstract. Recent studies have focused on identifying novel targeted agents in order to reduce the undesired side-effects of conventional chemotherapeutic agents on normal cells. However, even targeted therapies may exert certain negative effects on healthy tissues. The present systematic review was performed in order to evaluate the type and the incidence of side-effects in patients treated with everolimus. The PubMed and Scopus databases were searched using the following free words and MESH terms: 'everolimus' AND 'side-effects' OR 'toxicities' OR 'adverse events'. A total of 912 potentially relevant studies that were screened based on the title and abstracts were identified. A total of 731 were excluded as they did not fulfil the inclusion criteria. Of the 181 remaining studies included, the adverse events reported were obtained. The primary adverse events reported were stomatitis, leukopenia, anorexia, anaemia and fatigue. The majority of the patients reported adverse events limited to grade 1 or 2. On the whole, the data presented herein confirm the findings of previous studies on the relative safety of everolimus, a targeted therapeutic agent, which differs from that of conventional chemotherapy, and highlight the potential adverse events associated with the therapeutic use of everolimus.

Introduction

Traditional chemotherapy kills cancer cells using agents that target actively dividing cells. However, haematological cells, epithelial cells of the oral mucosa, intestinal mucosa, nasal mucosa, vaginal mucosa, nails and hair also exhibit high rates of division, and may thus be targeted by chemotherapy as well (1). The side-effects of chemotherapy are strictly related to the protocol used, the drug doses, the period of treatment and the health status of the patient. Thus, there is an increased focus on targeted therapies for the management of cancer (2). Targeted therapy aims to identify cancer-specific targets, thus reducing the incidence of side-effects. It was originally hoped that this type of therapy would exhibit considerably fewer issues, representing the 'holy grail' of cancer therapy; however, research has demonstrated that targeted therapeutic agents can in fact induce severe side-effects (1).

The mammalian target of rapamycin (mTOR) is a serine/threonine kinase that is involved in the PI3K/AKT/mTOR pathway (2). This pathway is important in the regulation of several cellular processes, including proliferation, cell survival and angiogenesis (3). The discovery that this pathway is dysregulated in several types of tumours has led to the development of several mTOR inhibitors. The first generation of mTOR inhibitors is represented by rapamycin and its analogues (2). These agents inhibit the action of MTORC1 through the binding of FK506 binding protein-12 (FKB12), which forms a ternary complex with mTOR (3). A total of four mTOR inhibitors are currently available: Sirolimus, everolimus, temsirolimus and ridaforolimus (4). These are large molecules (molecular weight (MW) ~1,000 kDa) that bind to FKBP-12 to generate a complex that blocks the mTOR protein kinase complex. These molecules are characterised by various side-effects compared with conventional chemotherapy (2,5,6). Everolimus in particular, is clinically used for the treatment of several solid tumours, such as advanced hormone receptor-positive human epidermal growth factor receptor 2 (HER-2)-negative breast cancer, renal cell carcinoma, neuroendocrine tumours of pancreatic origin, and sub-ependymal giant cell astrocytoma (2,3).

The following systematic review was performed in order to evaluate the most common side-effects of everolimus, and the incidence of the reported side-effects.

Materials and methods

Literature search. PubMed and Scopus were searched using the following combination of free words and MESH terms: 'everolimus' AND 'side-effects' OR 'toxicities' OR 'adverse events'. Only studies fulfilling the following inclusion

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criteria were considered eligible for inclusion in the present study: i) performed on human subjects; ii) reporting on the use of everolimus; iii) written in English and iv) reported the incidence of side-effects. Case reports and studies on animal models were excluded. For each study, the following information was recorded: Author, year of publication, title, therapeutic protocol, number of patients enrolled, number of events recorded for each toxicity, and grade of the events recorded. Data were independently extracted by three authors and assessed in a joint session.

Only the most numerically relevant toxicities and data related to patients who completed treatment were included. Data regarding patients that could not complete the treatment due to dose delays or discontinuations were excluded.

Results

The titles and abstracts of 912 potentially relevant studies were screened, of which, 731 were excluded as they did not fulfil the inclusion criteria. Of the 181 studies included, all the adverse events reported were recorded. The flow chart of the selection process is presented in Fig. 1. The results of the present meta-analysis revealed that the majority of adverse events reported were of grade 1 or 2, as shown in Table I.

For anaemia, 106 articles were read in full and 31 studies were excluded as they did not report the number of events. The overall incidence of anaemia was 24.4% (2,534 cases out of 10,386 patients). A total of 70 out of 75 articles also reported the grade: 2,470 cases out of 9,922 patients. The incidence of grade 1 or 2 anaemia was 17.8% (1,767/9,922), whereas the incidence of grade 3 or 4 anaemia was 7.1% (703/9,922) (Table SI).

For anorexia, 60 articles were read in full and 10 studies were excluded as they did not report the number of events. The overall incidence of anorexia was 25.2% (534 cases out of 2,120 patients). All the articles reported the grade: The overall incidence of grade 1 or 2 anorexia was 21.8% (463/2,120) and the overall incidence of grade 3 or 4 anorexia was 3.3% (71/2,120) (Table SII).

For asthenia, 38 articles were read in full text and 6 articles were excluded as they did not report the number of events. The overall incidence of asthenia was 20.6% (1,415 cases out of 6,847 patients). All the papers reported the grade: The incidence of grade 1 or 2 asthenia was 17.5% (1,201/6.847), whereas the incidence of grade 3 or 4 asthenia was 3.1% (214/6,847) (Table SIII).

For diarrhoea, 135 articles were read in full text and 25 articles were excluded as they did not report the number of events. The overall incidence was 22.3% (2,330 cases out of 10,436 patients). A total of 97 out of the 110 articles also reported the grade (2,029 cases out of 8,818 patients); the incidence of grade 1 or 2 diarrhoea was 20.4%, whereas the incidence of grade 3 or 4 diarrhoea was 2.6% (Table SIV).

For fatigue, 119 articles were read in full text and 18 studies were excluded as they did not report the number of events. The overall incidence was 23.7% (2,780 cases out of 11,436 patients). A total of 93 out of 101 articles also reported the grade (2,709 cases out of 10,923 patients). The incidence of grade 1 or 2 fatigue was 20% (2,187/10,923), whereas the incidence of grade 3 or 4 fatigue was 4.8% (522/10,923) (Table SV).

For hypercholesterolaemia, 58 studies were read in full text; 13 studies were excluded as they did not report the number of events. The overall incidence was 20.2% (1,078 cases out of 5,349 patients). A total of 44 out of 45 studies also reported the grade (1,074 cases out of 5,213 patients). The incidence of grade 1 or 2 hypercholesterolaemia was 19.3% (1,008/5,213), whereas the incidence of grade 3 or 4 hypercholesterolemia was 1.3% (66/5,213) (Table SVI).

For hyperglycaemia, 91 studies were read in full text and 10 studies were excluded as they did not report the number of events. The overall incidence was 16.9% (1,853 cases out of 10,878 patients). A total of 77 out of 81 studies also reported the grade (1,822 cases out of 10,135 patients). The incidence of grade 1 or 2 hyperglycaemia was 13.3% (1,347/10,135), whereas the incidence of grade 3 or 4 hyperglycaemia was 4.7% (475/10,135) (Table SVII).

For leukopenia, 50 studies were read in full text and 12 studies were excluded as they did not report the number of events. The overall incidence was 29.6% (495 cases out of 1,672 patients). A total of 35 out of 38 papers also reported the grade (476 cases out of 1,524 patients). The incidence of grade 1 or 2 leukopenia was 18.6% (283/1,524), whereas the incidence of grade 3 or 4 leukopenia was 12.6% (193/1,524) (Table SVIII).

For pneumonitis, 55 studies were read in full text and 5 studies were excluded as they did not report the number of events. The overall incidence was 10.1% (628 cases out of 6,201 patients). A total of 50 out of 55 studies also reported the grade (626 cases out of 6,096 patients). The incidence of grade 1 or 2 pneumonitis was 7% (429/6,096), whereas the incidence of grade 3 or 4 pneumonitis was 3.3% (197/6,096) (Table SIX).

For pruritus, 34 studies were read in full text and 2 studies were excluded as they did not report the number of events. The overall incidence was 12.1% (386 cases out of 3,187 patients). A total of 30 out of 32 studies also reported the grade (379 cases out of 3,130 patients). The incidence of grade 1 or 2 pruritus was 11.6% (365/3,130), whereas the incidence of grade 3 or 4 pruritus was 0.5% (14/3,130) (Table SX).

For pyrexia, 42 studies were read in full text and 7 were excluded as they did not report the number of events. The overall incidence was 15.4% (1,069 cases out of 6,961 patients). A total of 30 out of 35 studies also reported the grade (1,036 cases out of 6,692 patients). The incidence of grade 1 or 2 pyrexia was 14.2%, whereas the incidence of grade 3 or 4 pyrexia was 1.3% (85/6,692) (Table SXI).

For rash, 112 studies were read in full text and 14 studies were excluded as they did not report the number of events. The overall incidence was 22.7% (2,302 cases out of 10,114 patients). A total of 89 out of 98 studies also reported the grade (2,220 cases out of 9,273 patients). The incidence of grade 1 or 2 rash was 22.5% (2,082/9,273), whereas the incidence of grade 3 or 4 rash was 1.5% (138/9,273) (Table SXII).

For stomatitis, 181 studies were read in full text and 111 studies were excluded as they did not report the number of events. The overall incidence was 43.2% (3,568 cases out of 8,259 patients). A total of 62 out of 70 studies also reported the grade. Of the cases of stomatitis, 37.7% (2,959/7,854) were grade 1 or 2, whereas 6.8% (535/7,854) were grade 3 or 4 (Table SXIII).

Table I. Main systemic changes induced by everolimus therapy: Summary table.

Adverse effect	Adverse effects/cases (%)	Cases with grade/adverse effects (%)	Grade 1/2 % (cases)	Grade 3/4 % (cases)
Anaemia	2,534/10,386 (24.4)	2,470/9,922 (24.9)	1,767 (17.8)	703 (7.1)
Anorexia	534/2,120 (25.2)	534/2120 (25.2)	463 (21.8)	71 (3.3)
Asthenia	1,415/6,847 (20.6)	1,415/6,847 (20.6)	1201 (17.5)	214 (3.1)
Diarrhoea	2,330/10,436 (22.3)	2,029/8,818 (23)	1,797 (20.4)	232 (2.6)
Fatigue	2,780/11,436 (23.7)	2,709/10,923 (24.8)	2,187 (20)	522 (4.8)
Hypercholesterolemia	1,078/5,346 (20.2)	1,074/5,213 (20.6)	1,008 (19.3)	66 (1.3)
Hyperglycaemias	1,853/10,878 (16.9)	1,822/10135 (18)	1,347 (13.3)	475 (4.7)
Leukopenia	495/1,672 (29.6)	476/1,524 (31.2)	283 (18.6)	193 (12.6)
Pneumonitis	628/6,201 (10.1)	626/6,096 (10.3)	429 (7)	197 (3.3)
Pruritus	386/3,187 (12.1)	379/3,130 (12.1)	365 (11.6)	14 (0.5)
Pyrexia	1,069/6,961 (15.4)	1,036/6,692 (15.4)	951 (14.2)	85 (1.3)
Rash	2,302/10,114 (22.7)	2,220/9,273 (24)	2,082 (22.5)	138 (1.5)
Stomatitis	3,568/8,259 (43.2)	3,494/7,854 (44.5)	2,959 (37.7)	535 (6.8)
Thrombocytopenia	1,195/5,533 (21.8)	1,163/5,095 (22.8)	921 (18.1)	242 (4.7)
Emesis	883/5,913 (15)	858/5,578 (15.4)	781 (14)	77 (1.4)

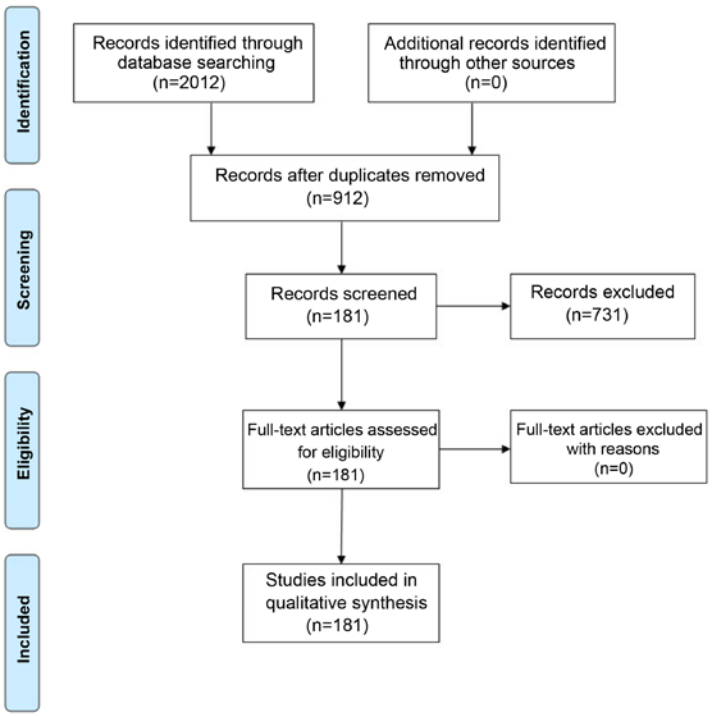

Figure 1. Flow-chart of the selection process.

For thrombocytopenia, 88 studies were read in full text and 14 studies were excluded as they did not report the number of events. The overall incidence was 21.8% (1,195 cases out of 5,533 patients). A total of 69 out of 74 studies also reported the grade (1,163 cases out of 5,095 patients) The incidence of grade 1 or 2 thrombocytopenia was 18.1% (921/5,095), whereas the incidence of grade 3 or 4 thrombocytopenia was 4.7% (242/5,095) (Table SXIV).

For emesis, 80 studies were read in full text and 8 studies were excluded as they did not report the number of adverse events. The overall incidence was 15% (883 cases out of 5,913 patients). A total of 67 out of 72 studies also reported the grade (858 cases out of 5,578 patients). The incidence of grade 1 or 2 emesis was 14% (781/5,578), whereas the incidence of grade 3 or 4 emesis was 1.4% (77/5,578) (Table SXV).

The majority of studies used a dose of 10 mg/day; only a few studies used a dosage of 2.5 mg/day and/or 5 mg/day. However, the number of cases treated with 2.5/5 mg/day was not sufficient to be used for statistical analysis for the evaluation of adverse events compared with 10 mg/day (Table SXVI).

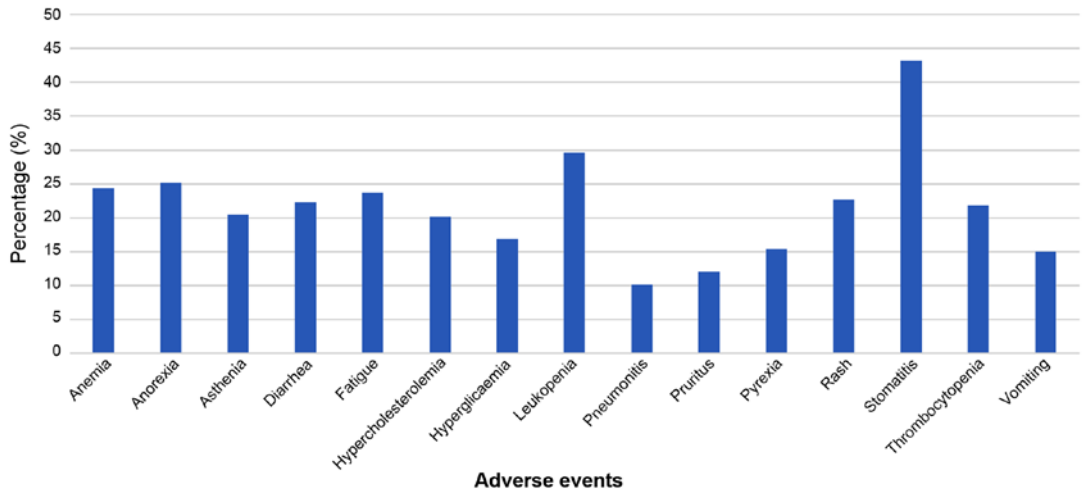

Figure 2. Graph shows the % of principal adverse effects due to the use of everolimus.

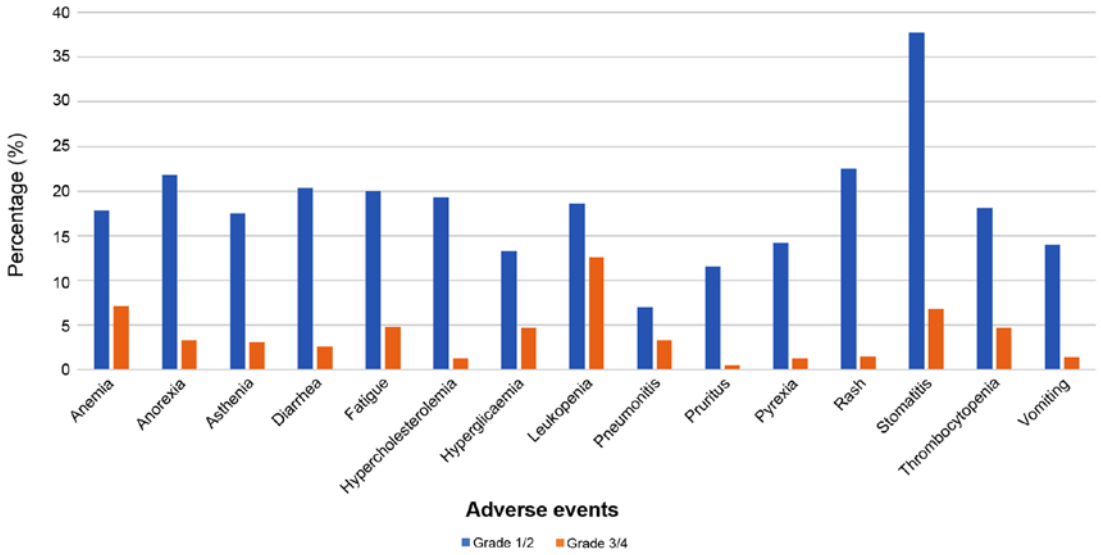

Figure 3. Graph shows the rapport between % of grade 1-2 and % of grade 3-4 for the principal adverse effects due to the use of everolimus.

The primary adverse events reported in the studies were stomatitis, leukopenia, anorexia, anaemia and fatigue (Fig. 2). The analysis of different grades revealed that for all adverse events, grade 1 and 2 side effects were more prevalent compared with grade 3 and 4 side effects (Fig. 3).

Discussion

The results of the present meta-analysis revealed that some of the most common adverse events reported were stomatitis, leukopenia, anorexia, anaemia and fatigue. Fortunately, the majority of events were classed as grade 1-2, which meant that they could be easily managed by the clinicians.

Targeted therapy acts by blocking a specific target in malignant cells. mTOR inhibitors belong to the class of signal transduction inhibitors. mTOR is implicated in several cellular processes that are essential for tumour progression, cell proliferation and survival and, therefore if combined with other anticancer drugs, mTOR inhibitors may function to sensitize the tumour cells to the primary anticancer agent. Sirolimus was the first mTOR inhibitor approved for clinical use (4). It is an antifungal agent already known for its immunosuppressive properties. However, its poor pharmacokinetic characteristics have led to the development of analogues, including everolimus, temsirolimus and ridaforolimus. These molecules differ from sirolimus in their C-40-O positions, with different pharmacokinetic and pharmacodynamic profiles, and have now been approved for the treatment of solid tumours, such as renal cell carcinoma, breast cancer and pancreatic neuroendocrine tumours.

Even if these drugs target specific signalling pathways that are upregulated in tumour cells, there is a possibility that this signalling pathway serves a physiological purpose in healthy cells, and thus the inhibition or activation of these pathways may induce adverse events. Some of these adverse events will be the same or similar to those observed in patients treated with conventional chemotherapy, whereas others may be unique to the targeted therapy.

Everolimus induces a wide range of side-effects that may limit the clinical use of this drug. The results of the present

meta-analysis demonstrated that most of these events were grade 1 or 2, as shown in Table I.

The National Cancer Institute grades anaemia as follows: Mild (grade 1), Hb between 10 g/dl and the lower physiological level; moderate (grade 2), Hb 8.0-9.9 g/dl; severe (grade 3), Hb <8 g/dl to 6.5 g/dl; and life-threatening (grade 4), Hb <6.5 g/dl (5). The incidence of anaemia due to everolimus therapy varied between 3.31% (6) and 100% (7). However, the mean value was 24.4% (2,534 cases out of 10,386 patients). mTOR inhibitors are immunosuppressive drugs that exert dose-dependent effects on haematopoiesis, thus potentially inducing anaemia. The specific mechanism by which everolimus induces anaemia is unclear; however, a pathogenic link has recently been suggested between anaemia induced by sirolimus and the appearance of an inflammatory state. Sánchez Fructuoso *et al* (8) suggested that the anaemia induced by everolimus, which is characterized by microcytosis, low serum iron levels despite prominent ferritinaemia, and high levels of C-reactive protein, was related to the induction of a chronic inflammatory state. Anaemia is the most common haematological side-effect in neoplastic patients (9). The anaemia induced by traditional chemotherapy is due to the malignant invasion of normal tissues with resultant blood loss and bone marrow infiltration, resulting in interruption of erythropoiesis and functional iron deficiency following inflammation (10). It is estimated that 70% of patients undergoing chemotherapy develop anaemia. The primary difference between everolimus-related anaemia and chemotherapy-related anaemia is that the incidence of grade 3 and 4 anaemia due to everolimus treatment is only 7.1%, whereas the incidence of mild or moderate anaemia (grade 1 and 2) in patients with solid tumours is ~60% of patients following platinum-based chemotherapy; severe (grade 3) anaemia in elderly patients with haematological malignancies may occur in up to 74% of patients with non-Hodgkin lymphoma following a standard cyclophosphamide/doxorubicin/vincristine/prednisolone regimen (11).

Everolimus-related anorexia (loss of appetite) is observed in 25.2% of all patients (534/2,120); the values range from 4.2% (12) to 93% (13). Anorexia is commonly associated with cancer or chemotherapy (14), results in significant weight loss, and may be the result of a decrease or a complete loss of appetite with or without nausea, vomiting, oral pain, diarrhoea and disturbances to taste (15). The National Cancer Institute grades anorexia as follows: Mild (grade 1), loss of appetite without alterations in eating habits; moderate (grade 2), oral intake altered without significant weight loss or malnutrition; severe (grade 3), associated with significant weight loss or malnutrition; life-threatening/disabling (grade 4), life threatening consequences (16). The primary difference between everolimus-related anorexia and chemotherapy-related anorexia is that the incidence of grade 3 and 4 anorexia due to everolimus treatment is only 3.3%, whereas the incidence of anorexia associated with traditional chemotherapy is 45% (17).

Cancer-related anorexia is often the result of an increase in the levels of pro-inflammatory cytokines or an increase in lactate levels. These two events can modulate central nervous system neurotransmitter cascades.

Asthenia (weakness) is an adverse event that is observed in 20.6% of patients treated with everolimus (1,415 cases out of 6,847 patients); and the reported incidence in individual studies varies between 2.4% (6) and 49.8% (18). Asthenia is the feeling of muscle tiredness; it is described as a lack of energy to move certain muscles or even all the muscles in the body. In oncological patients, asthenia is the most prevalent symptom; its pathophysiology remains relatively unknown, despite the significant impact it can have on quality of life (19). The incidence of asthenia associated with traditional chemotherapy is 35.7% (20).

Diarrhoea is observed in 22.3% of all patients treated with everolimus (2,330 cases out of 10,436 patients), with the incidence in individual studies ranging from 2% (21) to 72.7% (22). Chemotherapy-related diarrhoea may occur in 50-80% of patients, based on the specific chemotherapeutic regimen (23). Everolimus-related diarrhoea and chemotherapy-related diarrhoea have different features. Everolimus-related diarrhoea is prevalently grade 1 and 2 (20.4%), and rarely grade 3 and 4 (2.6%); chemotherapy-related diarrhoea is almost wholly grade 3-5 (30%), according to the Common Toxicity Criteria (24), particularly when treated with a bolus dose of 5-fluorouracil, or combination therapies including irinotecan and fluoropyrimidines (25). In patients with cancer, diarrhoea can lead to a loss of fluids and electrolytes, malnutrition followed by dehydration and hospitalization, eventually leading to cardiovascular problems and potentially death. Usually this adverse event is dose-related and may be associated with other characteristics of toxicity (25). Several drugs can induce diarrhoea, such as cyclophosphamide, daunorubicin, epirubicin, fluorouracil, gemcitabine, methotrexate, paclitaxel and vincristine. However, the pathophysiological mechanisms remain under investigation.

The analysis of the literature regarding fatigue related to everolimus treatment revealed that the incidence ranged from 5% (26) to 100% (26-28), with a mean of 23.7% (2,780 cases out of 11,436 patients). Fatigue due to chemotherapy is one of the most common problems amongst patients with cancer adversely affecting their quality of life. It has been estimated that fatigue affects up to 60% of patients treated with chemotherapy (27). The pathogenesis of cancer-related fatigue is not clear. Physical fatigue (inactivity, laziness and stress) and mental fatigue (reduced attention span, concentration, learning and short-term memory loss) are amongst the most common symptoms (28). A total of 10% of patients with fatigue due to traditional chemotherapy exhibit grade 3-4 fatigue (17), whereas 4.8% of everolimus-treated patients were reported to exhibit fatigue of grade 1-2 (17).

The incidence of hypercholesterolemia was found to be 20.2% following everolimus treatment, with the incidence in individual studies ranging from 3% (29) to 89% (30). Grade 1 and 2 hypercholesterolaemia are prevalent (present in 19.3% of patients), with grades 3 and 4 being reported in only 1.3% of the patients. Total cholesterol levels were slightly increased prior to the final cycles of chemotherapy compared with the prechemotherapy levels in several treatment protocols (31). At 6 months post-chemotherapy, the levels returned to baseline, except in taxane-treated patients (31).

Hyperglycaemia is observed in 16.9% (1,853 cases out of 10,878 patients) of all patients treated with everolimus, with the incidence in individual studies ranging from 1.7% (32) to 100% (33,34). The pathophysiology of hyperglycaemia in

association with mTOR develops via one of two mechanisms: i) A direct effect of mTOR inhibitors on the β cells of the pancreas causing a reduction in insulin secretion stimulated by glucose, resulting in an increase in apoptosis and other effects on cell viability and proliferation; ii) exaggeration of peripheral insulin resistance via mTOR inhibitors. In the muscles, there is a reduction in glucose absorption and a reduction in muscle mass. mTOR inhibitors facilitate gluconeogenesis in the liver and reduce the absorption of lipids in adipose tissue. Hyperglycaemia during chemotherapy occurs in 10-30% of the patients (35). Patients with grade 1 hyperglycaemia have glucose levels ≤160 mg/dl; patients with grade 2 hyperglycaemia have glucose levels 160-250 mg/dl; grade 3 hyperglycaemia is characterized by a glucose level 250-500 mg/dl; and grade 4 hyperglycaemia refers to a glucose level >500 mg/dl. Grades 2, 3 and 4 hyperglycaemias should be treated according to the consensus algorithm of the American Diabetes Association and European Association for the Study of Diabetes (36,37).

In addition to anaemia, mTOR inhibitors can cause other haematological toxicities, such as leukopenia and thrombocytopenia, that require regimen modifications or treatment suspension. Leukopenia and thrombocytopenia are caused by inhibition of signal transduction via glycoprotein 130 (β) chain, which is shared by certain cytokine receptors, granulocyte colony-stimulating factor and erythropoietin, resulting in stimulation of platelet, leukocyte and erythrocyte production (38). The incidence of leukopenia in patients subjected to everolimus treatment is 29.6% (495 cases out of 1,672 patients), with the incidence in individual studies ranging from 2.1% (12) to 90% (39). Neutropenia is one of the most serious haematological toxicities occurring during chemotherapy, and increases the susceptibility of patients to infection. Neutropenia generally occurs in 33.3% of patients undergoing chemotherapy (40).

The incidence of thrombocytopenia in patients treated with everolimus ranges from 0% (41) to 100% (33,42,43), with a mean of 21.8% (1,195 cases out of 5,533 patients). During traditional chemotherapeutic regimens, the incidence of chemotherapy-related thrombocytopenia varies depending on the treatment used; patients treated with gemcitabine and platinum-based regimens have the highest incidence of thrombocytopenia (44). The incidence of grade 3 and 4 thrombocytopenia was similar between everolimus therapy (4.7%) and traditional chemotherapy (5%) (17). The incidence of grade 1-2 thrombocytopenia undergoing traditional chemotherapy was higher than in patients being treated with everolimus (20 and 18.1%, respectively) (17).

Drug-related pneumonitis is one of the primary toxicities observed during anticancer systemic therapy and presents different radiographic manifestations on chest computed tomography (45). Everolimus-related pneumonitis has a mean incidence of 10.1% (628/6,201 patients), with the incidence in individual studies ranging from 0% (33) to 48.6% (43). Conventional chemotherapy-related toxicity can be dose-dependent, and may thus be observed at higher cumulative doses (bleomycin and carmustine) or several years after the end of therapy (cyclophosphamide, busulfan and carmustine) (46). The incidence of pneumonitis in patients treated with chemotherapy ranged between 1.5 and 50% (47).

Pruritus may be caused by standard chemotherapy, radiation therapy and immunotherapy. The occurrence of pruritus during conventional chemotherapy may be a sign of sensitivity to the drugs used; drugs used in immunotherapy may also cause dryness and itching. Everolimus can cause pruritus in 12.1% of all patients treated (386 cases out of 3,187 patients); the lowest reported incidence was 2.2% (6), whereas the highest was 91% (48). It is estimated that pruritus is observed in 10-25% of individuals treated with traditional chemotherapy (49).

Pyrexia was observed in 15.4% of all patients treated with everolimus (1,069 cases out of 6,961 patients); with the incidence ranging from 2% (29) to 44.4% (50). A study on pyrexia as a result of conventional chemotherapy reported an incidence of ~34% (51). The difference between everolimus-related pyrexia and chemotherapy-related pyrexia is that grade 3 and 4 pyrexia was only observed in 1.3% of patients treated with everolimus, whereas it was observed in 5% of patients treated with traditional chemotherapy (17).

The incidence of rash in patients undergoing everolimus treatment ranges from 2.7% (52) to 100% (53), with a mean incidence of 22.7%; instead, traditional chemotherapy caused rash in only 10% of all patients (17). Rash due to mTOR inhibitors can manifest as acneiform dermatitis that typically affects the neck or the upper extremities and starts as an inflammatory lesion (54).

Stomatitis is the most frequent adverse effect observed in patients treated with mTOR inhibitors. Stomatitis was observed in 43.2% of patients (3,568/8,259), with the incidence in individual studies ranging from 5.26% (29) to 100% (55). The pathophysiology of this type of stomatitis is not clear. Differences between mTOR inhibitor-related oral mucositis and classical oral mucositis include the clinical presentation and concomitant toxicities (56). mTOR inhibitor-associated stomatitis are aphthous-like lesions that are notably different from those related to chemotherapy or radiotherapy. The first manifestations observed are typically single or multiple shallow, well-circumscribed, round, painful ulcers localized in the non-keratinized mucosa and sometimes surrounded by an erythematous halo (57), whereas the second lesions formed are characterized by painful inflammation, erythema, swelling and ulcerations affecting the oral cavity, oropharynx and hypopharynx (58,59). Oral mucositis can be classified as grade 1 to 4. Oral pain during chemotherapy is quite common due to inflammation of the oral mucosa; certain drug combinations are more likely to cause mucositis compared with others. Oral mucositis usually occurs a few days after the commencement of therapy and subsides within a week. The degree of pain experienced may vary according to the severity of mucositis. Patients affected by oral mucositis are often neutropenic, and for this reason the pain can be worsened by the occurrence of oral mycosis, such as candidosis, which appears as whitish patches on the oral mucosa and on the surface of the tongue. Oral pain can also affect the sense of taste. The risk of developing oral mucositis is usually dose-dependent. Cytotoxic drugs able to induce oral mucositis include capecitabine, carboplatin, chlorambucil, cisplatin, cyclophosphamide, dacarbazine, dactinomycin, daunorubicin, doxorubicin, etoposide, fluorouracil, hydroxyurea, lomustine, melphalan, mercaptopurine, methotrexate, mitomycin, paclitaxel, raltitrexed, vinblastine and vincristine (60). Accordingly, at least

40% of patients treated with conventional chemotherapy may present with this condition (61,62). The frequency is higher (up to 80%) in patients undergoing haematopoietic cell transplantation (HCT), particularly myeloablative allogeneic HCT, and in those who are conditioned with radiation-containing regimens, and with the use of methotrexate for graft-versus-host disease prophylaxis. The administration of 5-fluorouracil is often associated with grade 3-4 oral mucositis (>15%).

Emesis (vomiting) was reported in 15% of patients treated with everolimus (883 cases out of 5,913 patients), with the incidence in individual studies ranging from 0% (33) to 75% (42). The incidence of emesis due to everolimus treatment was 15%, whereas emesis due to chemotherapy was reported in ~30% of individuals. The severity of emesis differs according to the specific chemotherapeutic drugs used, and it is classified as high-risk (>90% of patients are likely to be affected), moderate-risk (30-90% of patients affected), low-risk (10-30%) and minimal-risk (<10% of patients affected). Furthermore, females are more at risk than males, and younger individuals are more at risk than older individuals.

Even if patients treated with everolimus appear to exhibit fewer of the 'standard' toxicities usually associated with chemotherapy (for example, emesis), there is an increase in a new group of frequently occurring side-effects, including dermal, vascular and gastrointestinal toxicities, which may be caused by receptor cross-reactivity or the presence of receptors on or in non-cancerous cells. Moreover, the incidence of side-effects may vary depending on the tumour type, likely due to differences in the complex tumour biology. Other features involved in the treatment response may be age, sex and ethnicity of patients treated. Further research is required for more accurate comparisons of side effects provoked by targeted therapy and those caused by conventional chemotherapy.

In conclusion, the role of the oncologists is not limited to the treatment/therapy of the disease; instead, they must aim to prolong survival, control symptoms and improve the quality of life of the patients. Targeted therapy is a relatively novel therapeutic approach to the management of several types of tumours. Among these new drugs, everolimus expands the therapeutic armamentarium available to fight cancer and other diseases. The aim of the present study was to evaluate the quality of life of patients undergoing everolimus therapy through the evaluation of side effects related to everolimus, compared with conventional chemotherapy. Despite a global reduction in side-effects with the intake of everolimus (Table SXVII), certain adverse effects, such as stomatitis and rash, were more commonly related to this type of therapy compared with traditional chemotherapy. However, the majority of adverse effects reported in patients treated with everolimus were grade 1 and 2, whereas those induced by conventional chemotherapy were primarily grade 3 and 4.

Thus, it may be easier to manage everolimus-associated side-effects compared with those of traditional chemotherapy. However, it is necessary to perform trials with larger cohorts to better evaluate the safety of everolimus.

As regards limitations, the present meta-analysis could not be registered on Prospero, and the study was based on literature available from only two databases. Future prospective studies are required to improve the accuracy of the results. Furthermore, only studies written in the English language were included. The online search retrieved ~1,100 duplicates that were identified and excluded by EndNote X9. Only numerically relevant adverse events were included, as this systematic review was intended to be easily readable by clinicians, and the data are based entirely on previous studies. These shortcomings are acknowledged as limitations and further studies are required to improve the quality of the results and to include all adverse events that were reported in clinical trials.

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Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

CA extracted and analysed the data, and contributed to the conception of the hypothesis for the study. MEB extracted and analysed the data, and contributed to the preparation of the manuscript. VCAC analysed the data. GT contributed to data analysis and revised the manuscript. KZ contributed to data extraction and contributed to the preparation of the manuscript. SL contributed to data analysis revised the manuscript. LLM extracted and analysed the data, and approved the submitted version. All authors read and approved the final manuscript. CA and LLM confirm the authenticity of all the raw data.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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