Risk of Anemia Attributable to Everolimus in Patients with Cancer: A Meta-analysis of Randomized Controlled Trials

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Abstract. *Background: Everolimus, an inhibitor of mammalian target of rapamycin (mTOR) used for the treatment of various solid tumors, is associated with anemia, which can lead to morbidity and treatment interruption or discontinuation. Because the underlying causes of anemia can be multifactorial, we performed a meta-analysis of randomized controlled trials (RCTs) to determine the overall risk of anemia specifically attributable to everolimus in cancer patients. Materials and Methods: We searched the PubMed database and abstracts presented at the American Society of Clinical Oncology annual meetings up to May 2014 for relevant studies. Eligible studies included RCTs in which everolimus alone or in combination with other agents was compared to placebo alone or with other agents in patients with cancer. Summary incidences, relative risks (RR), and 95% confidence intervals (CI) were calculated using a random- or fixed-effects model depending on the heterogeneity of the included trials. The attributable risk was determined by the incidence with everolimus minus that without everolimus in controls. Results: A total of nine RCTs with 3,678 patients (everolimus, n=2,162; controls, n=1,516) were included in our analysis. In comparison with controls, everolimus significantly increased the risk of all-grade (RR=2.18, 95% CI=1.56-3.04, p<0.001) and high-grade anemia (RR=2.63, 95% CI=1.35-5.15, p<0.001). The summary incidences of all-grade (grades 1-4) and high-grade (grades 3-4) anemia in patients treated with everolimus were 32.1% (95% CI=17.5-51.3%) and 6.9% (95% CI=4.1-11.3%) respectively, with 13.3% (95% CI=10.0-17.5%) and 4.7% (95% CI=2.8-7.7%) specifically attributable to everolimus. Risk factors of high-grade anemia attributable to everolimus included tumor type (p=0.012), with the highest seen in renal cell carcinoma (8.0%, 95% CI=5.3-11.9%), and chemotherapy (p<0.001). Conclusion: There is a substantial risk of all-grade and high-grade anemia attributable to everolimus therapy for cancer.*

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The mammalian target of rapamycin (mTOR) is a serine/threonine protein kinase that has ubiquitous expression in mammalian cells, and plays a major role in cellular signaling cascades (1-3). Overexpression of mTOR has been implicated in the pathogenesis of numerous malignancies, leading to the development of first-generation mTOR inhibitors (everolimus, temsirolimus, and ridaforolimus) (3).

Everolimus is currently approved as a treatment for advanced renal cell carcinoma (RCC) after failure with sorafenib and sunitinib, advanced hormone receptor-positive human epidermal growth factor receptor-2-negative breast cancer in combination with exemestane, progressive pancreatic neuroendocrine tumors (PNET), and subependymal giant cell astrocytoma (SEGA) in pediatric and adult patients. Once-a-day oral dosing and a relatively favorable safety profile make it a popular therapy for patients with cancer.

Common adverse events associated with everolimus include stomatitis, rash, hyperglycemia, hyperlipidemia, fatigue and hematological toxicity (3-4). Anemia is a serious adverse effect, leading to morbidity and treatment interruption or discontinuation by many patients. Because anemia may result from multiple factors, including underlying diseases and concurrent use of other drugs, the specific impact of everolimus on the development of anemia has not been defined.

In this study, we performed a meta-analysis of randomized controlled trials (RCTs) in which everolimus was compared to controls, and determined the overall risk of all-grade and high-grade anemia specifically attributable to everolimus in patients with cancer.

Table I. *Characteristics of randomized controlled trials included in the meta-analysis.*

Source(Ref)	Trial phase	Enrolled	Analyzed	Median follow-up (months)	Underlying malignancy	Concurrent treatment	Everolimus dose per od (mg/day)	Study quality[a]
Yao *et al*., 2011 (15)	III	410	410	17	Pancreatic NET	N/A	10	5
Bissler *et al*., 2013 (11)	III	118	118	NA	Angiomyolipoma	N/A	10	5
Ohtsu *et al*., 2013 (13)	III	872	656	14.3	Gastric cancer	BSC	10	5
Motzer *et al*., 2010 (12)	III	422	416	NA	Renal cell carcinoma	BSC	10	5
Baselga *et al*., 2012 (10)	III	724	720	NA	Breast cancer	exemestane	10	3
Baselga *et al*., 2009 (9)	II	270	269	NA	Breast cancer	letrozole	10	5
Pavel *et al*., 2011 (14)	III	429	429	28	NET	octreotide	10	5
Andre *et al*., 2014 (7)	III	569	562	20	Breast cancer	trastuzumab vinorelbine	5	5
Bachelot *et al*., 2012 (8)	II	111	111	24	Breast cancer	tamoxifen	10	5

NA, Data not available; NET, neuroendocrine tumor; BCS, best supportive care; N/A, not applicable. [a]Study quality was assessed on the 7-item Jadad scale, with a score range of 0 to 5.

Materials and Methods

Data source. The PubMed database (www.pubmed.gov) was independently searched (from 01/01/1998 to 06/01/2014) using the key words "everolimus" and "anemia". We searched for abstracts presented at the American Society of Clinical Oncology (ASCO) annual conferences (2004-2013) using the same key words. Abstracts were reviewed for complete adverse event information regarding anemia. Each publication was reviewed to ensure that the most recent and up-to-date version was identified to avoid data collection from a duplicate publication of a clinical trial.

Study selection. In order to determine the specific contribution of everolimus to the risk of anemia, we selected phase II and III prospective RCTs in which the only difference between the two arms was everolimus; thus everolimus alone or in combination with other agents was compared to placebo or other drugs for patients with cancer. All non-randomized clinical trials were excluded. Phase I trials were also excluded due to the use of multiple experimental doses.

Each trial was required to provide the number of and/or percentage of patients with all-grade (grade 1-4) and high-grade (grade 3-4) adverse effects as defined by the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE). The Jadad Score was used to assess the quality and integrity of each selected clinical trial (6). The Jadad Score is based on a 7-item scale that has a score range from 0-5 with points given for declaration of randomization, appropriate method of randomization, description of double-blind trial design, appropriate double-blinding, and description of dropouts and withdrawals (6). A score of at least 3 was required for inclusion in the analysis.

Clinical end-points. The severity of anemia was reported based on hemoglobin values in the NCI-CTCAE version 3.0. In version 3.0: grade 1, < lower limit of normal-10.0 g/dl; grade 2, <10-8.0 g/dl, grade 3, 8-6.5 g/dl, grade 4, <6.5 g/dl.

Statistical analysis. All statistical analyses were performed using Comprehensive MetaAnalysis program version 2.0 (Biostat, Englewood, New Jersey, United States of America). The number of patients with all-grade and high-grade anemia, and the number of patients receiving everolimus or of controls were extracted from eligible clinical trials. Additional data collected included the specific tumor type studied, and whether everolimus was administered in combination or as a single agent, total cumulative all-grade anemia, cumulative high-grade anemia and percentage of discontinuation secondary to anemia. The RR of anemia among patients assigned to everolimus was calculated and compared to that of patients assigned to the control arm. In each study, the proportion of patients with anemia was calculated and the 95% confidence interval was derived. We also calculated the risk attributable to everolimus for both all-grade and high-grade anemia by subtracting the incidence without everolimus in controls from the incidence with everolimus in the same trial.

For meta-analysis, both fixed-effects (weighted with inverse variance) and random-effects model were considered. Prior to the meta-analysis, Cochran's Q statistic was calculated to assess the heterogeneity among the proportions of the included trials. For a *p*-value of less than 0.1, the assumption of homogeneity was considered invalid and the random-effects model was used; if the assumption of homogeneity was valid, both the fixed-effects and random-effects model results were used. We used Begg's and Egger's tests to determine the presence of publication bias regarding the primary endpoint (RR of all-grade and high-grade anemia). A two-tailed *p*-value of less than 0.05 was considered to be statistically significant.

Results

Search results. Our literature search yielded a total of 379 potentially relevant studies of everolimus. The PubMed and ASCO annual meeting abstracts identified 25 RCTs, of which 16 studies were excluded after further examination (Figure 1). RCTs in which both the comparator and control arms received everolimus or there was insufficient data regarding adverse effects were excluded. Overall, a total of nine RCTs of everolimus were included in our final analysis (6-14) (Table I). These included phase III (n=7) and phase II (n=2) trials.

Through an independent review, eight trials received the highest Jadad score of 5 for study quality (7, 9-15). A score of 3 was given to one trial (8).

Patients. A total of 3,689 patients from the nine RCTs were available for analysis: 1,890 patients received everolimus at a dose of 10 mg by mouth once a day (8-15), and 280 patients were given 5 mg by mouth once a day (7). Everolimus was administered with tamoxifen to 54 patients (8). Combinational therapy with exemestane and everolimus was given to 485 patients (10). Everolimus with octreotide was given to 216 patients (14), and 138 patients received everolimus with letrozole (9). Trastuzumab and vinorelbine with everolimus was administered to 280 patients (7). Alternatively, everolimus was used as mono-therapy in 997 patients (11-15). Solid tumors treated with everolimus included PNET (14-15), angiomyolipoma associated with tuberous sclerosis (11), advanced gastric cancer (13), metastatic RCC (12), and advanced breast cancer (7-10).

Incidence of all-grade and high-grade anemia. For analysis, all-grade anemia data was available for a total of 2,170 patients treated with everolimus. Incidence of all-grade anemia ranged from 11.7% to 92.0%, with the lowest incidence being found in a multicenter phase II trial investigating patients with estrogen receptor (ER)-positive breast cancer (9), and the highest incidence derived from a phase III trial in patients receiving everolimus with best supportive care for metastatic RCC (12). The summary incidence of all-grade anemia from the nine trials was 32.1% (95% CI=17.5-51.3%) using the random-effects model (heterogeneity test: Q=407.82, I^2=98.04, p<0.001).

High-grade anemia is associated with significant morbidity, and may require transfusion and dose modification of everolimus. Data were available for a total of 2,170 patients treated with everolimus. Incidence of high-grade anemia ranged from 0.4% to 18.9%, with the lowest incidence being found in the aforementioned phase II trial investigating ER-positive advanced breast cancer (9), and the highest derived from a phase III trial in patients receiving 5 mg/day everolimus with trastuzumab and vinorelbine for ER-positive, trastuzumab-resistant, advanced breast cancer (7). The summary incidence of high-grade anemia from the nine trials was 6.9% (95% CI=4.1-11.3%) using the random-effects model (heterogeneity test: Q=71.99, I^2=88.89, p<0.001).

Relative risk of all-grade and high-grade anemia. The RR of all-grade and high-grade anemia associated with everolimus was calculated to ascertain the specific contribution of the drug without the influence of confounding factors such as underlying malignancy, co-morbidities and concurrent use of other therapies. In comparison with controls, everolimus significantly increased the risk for developing all-grade anemia (RR=2.18, 95% CI=1.56-3.03, p<0.001) using the random-effects model (heterogeneity test: Q=51.45, I^2=84.45, p<0.001) (Figure 2A). The risk for developing high-grade anemia was also increased (RR=2.63, 95% CI=1.34-5.15, p<0.001) using the random-effects model (heterogeneity test: Q=16.14, I^2=62.83, p<0.05) (Figure 2B).

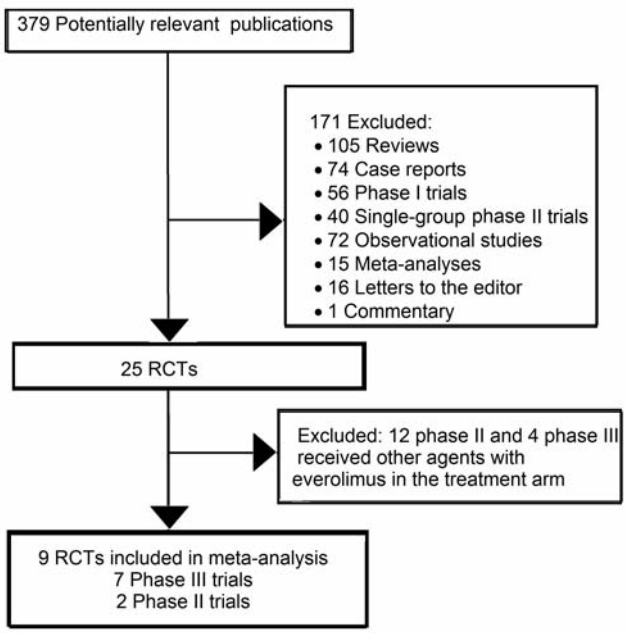

Figure 1. *Selection of randomized controlled trials (RCTs) included in the meta-analysis*.

Risk of anemia attributable to everolimus. We further determined the absolute risk specifically attributable to everolimus (AR) by calculating the difference between the incidences with and without everolimus. The incidence of all-grade anemia attributable to everolimus ranged from 6.7% to 33.4%, with the lowest risk being identified in a phase III trial of advanced gastric cancer (13), and the highest in a phase III trial involving patients with ER-positive, human epidermal growth factor receptor-2-negative, breast cancer (8) (Figure 3A). The summary incidence of all-grade anemia attributable to everolimus was 13.3% (95% CI=10.0-22.2%) using the random-effects model (heterogeneity test: Q=46.22, I^2=82.20, p<0.001). A sub-group analysis of all-grade anemia secondary to everolimus was performed. The risk attributable to everolimus varied significantly with tumor type (p=0.01), with the lowest risk in patients with advanced gastric cancer (AR=6.7%, 95% CI=4.7-9.5%) and the highest risk in breast cancer (AR=17.2%, 95% CI=10.8-26.3%) (7-10,13). No significant variation was found for everolimus when used as a single agent *versus* it being combined with other agents (p=0.17). However, a significantly increased risk attributable to everolimus was noted when it was combined with vinorelbine

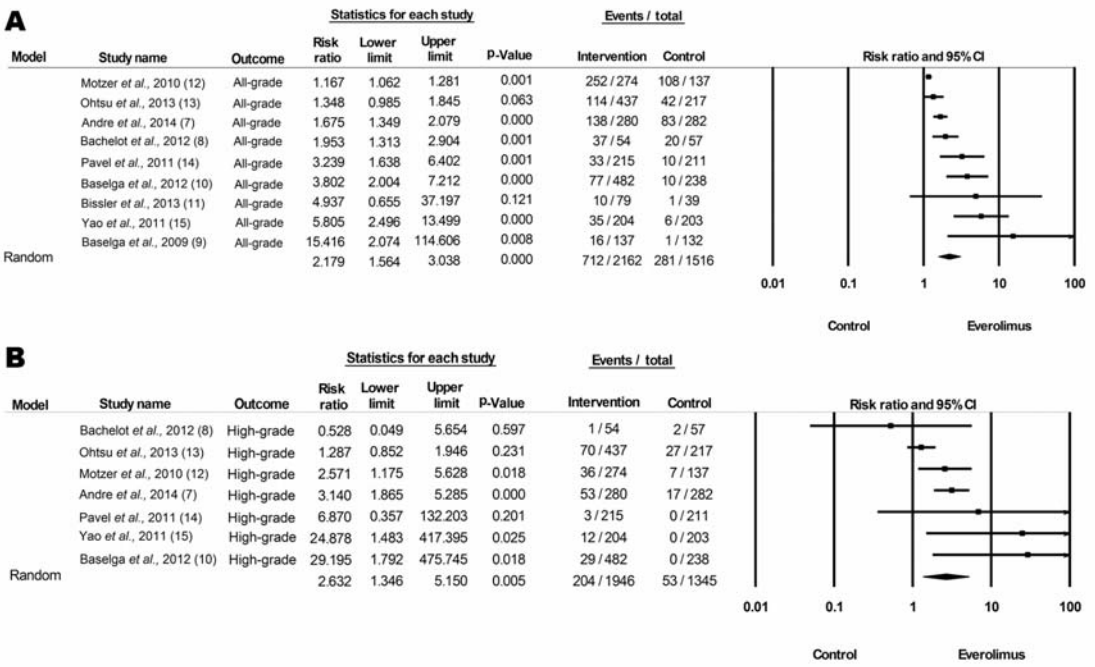

Figure 2. *Relative risks (RR) of all-grade (a) and high-grade (b) anemia associated with everolimus vs. that of controls. CI, Confidence interval. The RRs were calculated using the random-effects model. The RR and 95% confidence interval (CI) for each trial and the final combined results are demonstrated numerically on the left and graphically as a forest plot on the right. For individual trials: closed square, incidence; lines, 95% confidence interval; diamond plot, overall results of the included trials.*

and trastuzumab (7), compared to being given as a single-agent or in combination with non-chemotherapy agents ($p<0.05$).

The incidence of high-grade anemia attributable to everolimus ranged from 0.4% to 12.9%, with the lowest risk being found in a phase II trial in ER-positive breast cancer (9), and the highest derived from a phase III trial in patients with ER-positive, trastuzumab-resistant breast cancer (7) (Figure 3B). The summary incidence of anemia attributable to everolimus was 4.7% (95% CI=2.8-7.7%) using the random-effects model (heterogeneity test: Q=41.58, I^2=80.76, $p<0.001$). As with all-grade anemia, the risk of high-grade anemia attributable to everolimus varied significantly with tumor type ($p=0.012$), with the highest risk being seen in metastatic RCC (AR=8%, 95% CI=5.3-11.9%), and the lowest in angiomyolipoma (AR=0.6%, 95% CI=0-9.2%) (11-12). No significant variation in attributable risk was found comparing everolimus monotherapy *versus* combination with other agents ($p=0.58$), however, an increased risk for high-grade anemia attributable to everolimus was noted when it was combined with vinorelbine and trastuzumab, compared to when being combined with non-chemotherapy agents ($p<0.001$).

Discussion

This meta-analysis of RCTs has shown a significantly increased risk of anemia specifically attributable to everolimus in patients with cancer. The summary incidences of all-grade and high-grade anemia were 32.1% (95% CI=17.5-51.3%) and 6.9% (95% CI 4.1-11.3%), respectively, with 13.3% (95% CI=10.0-17.5%) and 4.7% (95% CI=2.8-7.7%) specifically attributable to everolimus. Everolimus significantly increased the risk of both all-grade (RR=2.18, 95% CI=1.56-3.04, $p<0.001$) and high-grade anemia (RR=2.63, 95% CI=1.35-5.15, $p<0.001$). Our results demonstrate that anemia secondary to everolimus is a common adverse effect; this may cause significant morbidity and treatment interruption/dose reduction, and prevent sustained treatment in patients with cancer.

Anemia is a common manifestation of cancer, and is an independent prognostic factor for increased mortality (16). Relevant to our study, a low hemoglobin value was associated with shorter overall survival in the RECORD-1 trial, which compared everolimus to placebo in metastatic RCC (12). As a frequent cause of cancer-related fatigue, anemia has a negative impact on the quality of life of patients (17-19). Systemic chemotherapy is a well-recognized risk factor for the development of anemia (20). In the prospective European Cancer Anemia Study, which included over 15,000 patients with cancer, the incidence of anemia (Hb <10 g/dl) was 53.7% in patients who received chemotherapy with/without radiation (21). In addition to mTOR inhibitors, tyrosine kinase inhibitors (TKIs), anti-epidermal growth factor receptor (EGFR), and anti-vascular

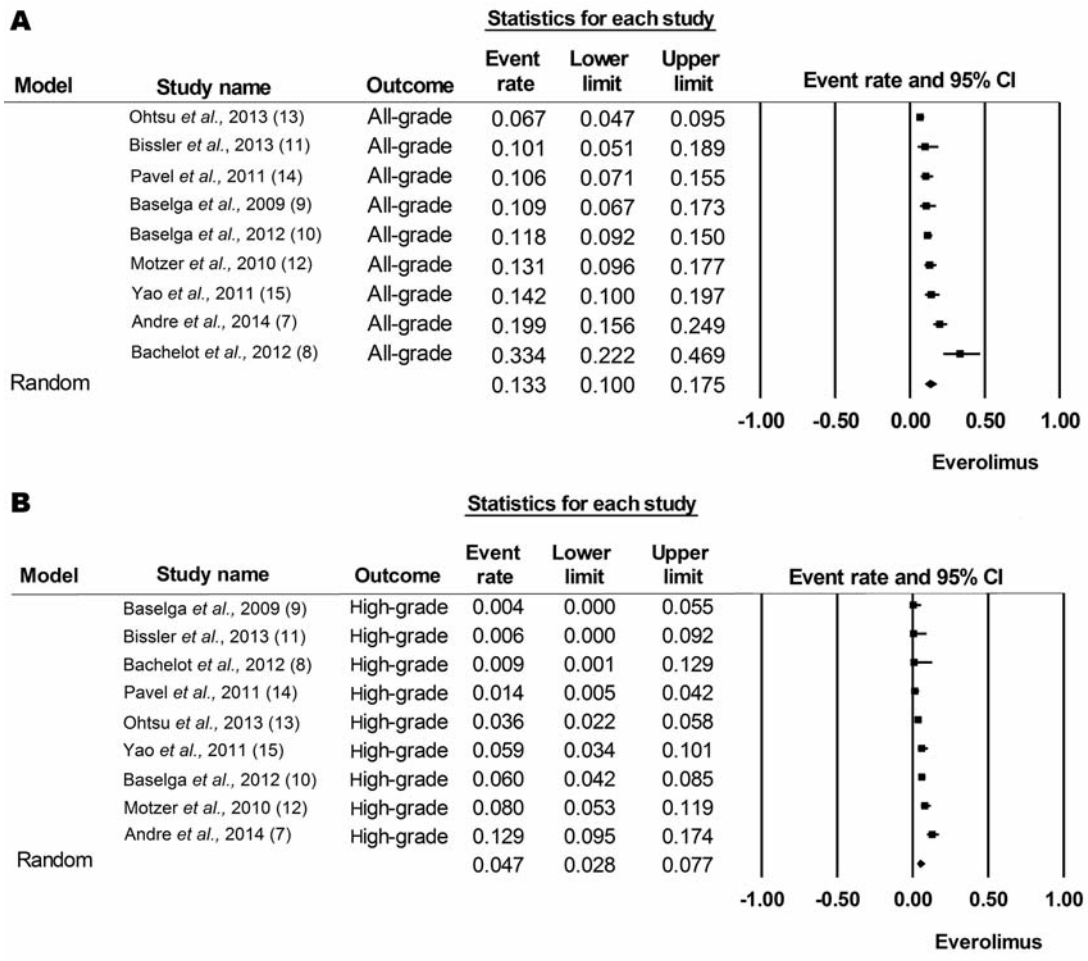

Figure 3. *Risk of all-grade and high-grade anemia attributable to everolimus. The risk attributable to everolimus for all-grade (a) and high-grade (b) anemia was calculated using the random-effects model. The attributable risk and 95% confidence interval (CI) for each trial and the final combined results are demonstrated numerically on the left and graphically as a forest plot on the right. For individual trials: closed square, incidence; lines, 95% confidence interval; diamond plot, overall results of the included trials. TS, Tuberous sclerosis; NET, neuroendocrine tumors; P-NET, pancreatic neuroendocrine tumors; RCC, renal cell carcinoma; CI, confidence interval.*

endothelial growth factor (VEGF) receptor-targeted agents are increasingly being associated with a risk for anemia (17). The risk of anemia attributable to everolimus in patients with solid tumors who are previously or concurrently treated with systemic chemotherapy has not been well commented on. The majority of anemia adverse effects in the included clinical trials were low-grade (grade 1-2). A retrospective analysis of everolimus efficacy and safety in metastatic RCC found anemia to be both a frequent cause of high-grade (≥3) adverse events (27%) and a reason for dose reduction or interruption (22). Because of the relatively recent introduction of everolimus, real-world clinical experience is limited. In a study outside of the regulatory trial setting that evaluated everolimus in PNET, drug discontinuation due to toxicity occurred in 8.9% of patients, and high-grade (≥3) anemia (5.3%) was one of the most common severe adverse events (23). This emphasizes that with increasing use of everolimus, clinicians are likely to be faced with the challenge of managing anemia secondary to everolimus, a drug that requires consistent dosing for optimal benefit. As opposed to systemic chemotherapy, the onset of anemia secondary to everolimus is highly variable as early as within the first three months of treatment to more than one year from the time of everolimus introduction (24). Thus, monitoring of hemoglobin should be performed periodically throughout everolimus treatment.

In a previous systematic review and meta-analysis of hematological toxicities in patients with solid tumors treated with everolimus, an increased risk of all-grade (RR=9.19, 96% CI=4.51-18.70, $p<0.0001$), and high-grade (RR=7.46, 95% CI=2.58-21.61, $p<0.0001$) anemia was seen (25). It should be noted that this analysis was not limited to RCTs and included

single-arm studies (25). In another more recent meta-analysis of hematological toxicity that was not restricted to but included 11 RCTs, the use of mTOR inhibitors (temsirolimus and everolimus) was associated with a significantly increased risk of all-grade anemia (RR=2.05, 95% CI=1.52-2.77, $p<0.001$) and high-grade anemia (RR=1.57, 95% CI=1.20-2.05, $p<0.001$) (26). Our analysis is novel through focusing on the risk of anemia specifically attributable to everolimus based on data from high-quality RCTs. The highest incidence of all-grade anemia was seen in patients with ER-positive, human epidermal growth factor receptor-2-negative, breast cancer (8), and for high-grade anemia in ER-positive, trastuzumab-resistant breast cancer (7).

The AR of all-grade anemia due to everolimus varied significantly with regard to tumor type, with the greatest risk being seen in breast cancer. In three out of the four breast cancer RCTs, a large percentage of patients had previously received systemic chemotherapy, increasing the risk of anemia with everolimus treatment (7-8, 10). Approximately 84% and 46% of patients had received two or more different lines of systemic chemotherapy prior to enrollment in the BOLERO-2 and BOLERO-3 trials respectively (7, 10). The AR of high-grade anemia due to everolimus was also high in breast cancer, however the greatest risk was seen in metastatic RCC. In the RECORD-1 trial, patients with metastatic RCC had been treated with the VEGF TKIs sorafenib (29%) and sunitinib (45%) or both (26%) prior to receiving everolimus (12). The VEGF TKIs have been shown to increase the risk of anemia in patients with cancer (17). This emphasizes that selected individuals previously treated with extensive systemic chemotherapy and targeted-agents with hematological toxicity profiles are at increased risk for development of anemia and require closer follow-up during everolimus usage. Pre-clinical studies have shown that mTOR inhibition enhances the antitumor effect of trastuzumab and vinorelbine (27-28). Enhanced efficacy of this combination may also come with heightened hematological toxicity. Based on a phase I dose escalation study, the BOLERO-3 investigators chose to administer a lower dose of everolimus (5 mg/day) compared to the higher dose (10 mg/day) approved for other indications (7, 29). Incidence and severity of anemia may be even greater with everolimus at 10 mg/day in combination with vinorelbine and trastuzumab.

Anemia secondary to targeted therapy is multifactorial, and can be related to impaired iron metabolism, reduced red blood cell production in the bone marrow, elevated levels of inflammatory cytokines, blood loss, reduced survival *via* hemolysis, and suppression of erythropoietin (30-33). The precise etiology for anemia secondary to everolimus is poorly understood. The myelosuppressive effects of mTOR inhibitors are potentially due to inhibition of signal transduction of the glycoprotein 130-β-chain expressed on various cytokine receptors, including interleukin-11, granulocyte colony-stimulating factor, and erythropoietin (33-35). *In vivo* studies have shown that mTOR inhibition leads to microcytosis with low serum iron levels despite high ferritin levels, consistent with a profile of anemia of chronic disease (33-35). In a recent analysis of hematological toxicity associated with everolimus use in patients with breast cancer, a significant drop in red cell volume and hemoglobin concentration was seen at 14 days from the time of everolimus initiation, with progressive decline over time (36). The reversibility of anemia due to everolimus was also seen by an increase in mean red cell corpuscular volume and mean corpuscular volume two months after everolimus discontinuation (36).

Treatment options for anemia in patients with cancer includes blood transfusion and additional agents that reduce transfusion requirements: iron supplementation, and erythropoiesis-stimulating agents (ESAs) (17, 37). Blood transfusion is effective because of its rapid and reliable effect, however, it also comes with risks including transfusion-related reactions, congestive heart failure, infection, and iron overload with repetitive use (30, 38). The ESAs epoetin and darbepoetin have been shown to reduce the need for blood transfusion requirements and improve quality of life in patients with solid tumors receiving chemotherapy (30, 9-41). They are not recommended for the treatment of anemia secondary to cancer in patients not receiving myelosuppressive chemotherapy due to an increase in mortality risk and risk for tumor progression (39, 42). Prior to ESA treatment for chemotherapy-associated anemia, alternative causes of anemia such as iron deficiency, vitamin B12 deficiency, occult blood loss, and renal insufficiency should be ruled out. For chemotherapy-associated anemia, epoetin or darbepotein can be given when hemoglobin is less than 10 g/dl (39). Caution with use of ESAs for hemoglobin levels above 10 g/dl is advised due to an increased risk for thromboembolic events and hemoglobin levels should be increased to the lowest level to reduce the need for transfusion (39, 42). Unfortunately, the most recent guidelines from the National Cancer Comprehensive Network and American Society of Hematology are restricted to chemo-therapy-associated anemia, with a clear absence of direction for anemia secondary to use of targeted agents (39, 42). Based on expert opinion and clinical experience, everolimus dose reduction or interruption is not necessary for low-grade (grade 1-2) adverse events (30, 37). However, discontinuation is warranted for grade 3 adverse events, and can be restarted at a lower dose after recovery (27, 33). In the setting of life-threatening toxicity, everolimus should be permanently discontinued (30, 37). In our analysis of the included RCTs, the investigators did not provide information regarding the number of dose reductions or drug discontinuation specifically due to anemia. Of note, in the summary of product characteristics for everolimus, dose adjustment recommen-dations are available for the occurrence of thrombocytopenia and neutropenia, but not for anemia (43).

This meta-analysis has several limitations. Results may have been limited by the accuracy of the grading of severity of anemia in individual RCTs. Another limitation is inclusion of a phase III trial that administered everolimus at lower dose than approved (7). However, instead of a lower incidence of anemia, the clinical trial that administered a lower dose of 5 mg by mouth once a day had the highest AR for high-grade anemia (7). We chose to focus on the risk of anemia attributable to everolimus, however, anemia has been shown to be a common adverse effect in RCTs of other first-generation mTOR inhibitors (44-45). For example, in a RCT evaluating temsirolimus in metastatic RCC, all-grade and high-grade anemia were 45% and 20% respectively (44). In a phase III RCT of patients with metastatic sarcoma who had previously received chemotherapy, increased incidence was found for both all-grade (28%) and high-grade (25%) anemia with ridaforolimus compared to placebo (45). Future analysis of the risk of anemia attributable to other first-generation mTOR inhibitors would be of great interest.

Conclusion

Our meta-analysis has demonstrated a substantial risk of all-grade and high-grade anemia attributable to everolimus use in patients with cancer, and the toxicity of everolimus may vary with tumor type and concurrent therapies. Further research is necessary to clarify the pathogenesis of anemia secondary to mTOR inhibition and to reduce the risk. Currently, everolimus discontinuation or interruption and dose reduction in the setting of anemia is limited to expert opinion and clinical experience. It is important to exclude other causes of anemia in these patients before attributing it entirely to everolimus. Evidence-based guidelines are critically needed due to the increasing use of everolimus in patients with cancer.

Conflicts of Interest

Dr. Shenhong Wu is a speaker for Novartis, Pfizer, and Astella-Medivation. All other Authors have no other declarations. No funding was provided for this study.

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