Renal toxicity with mammalian target of rapamycin inhibitors: A meta-analysis of randomized clinical trials

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Abstract

A meta-analysis of randomized clinical trials (RCT) was done to determine the relative risk (RR) of acute kidney injury (AKI) with the use of mammalian target of rapamycin (mTOR) inhibitors. Citations from PubMed/Medline, clinical trials.gov, package inserts and abstracts from major conferences were reviewed to include RCTs comparing arms with or without mTOR inhibitors. The RR of all grade AKI in patients taking mTOR inhibitors compared to patients not on mTOR inhibitors was 1.55 (95% CI: 1.11 to 2.16, P=0.010). There was no significant difference in the risk of high-grade AKI for the two groups (RR=1.29, P=0.118, 95% CI: 0.94 to 1.77). There was no significant difference in the incidence rates for either all grade or high-grade AKI between the two groups. There was no publication bias and the trials were of high quality per Jadad scoring.

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Introduction

Mammalian target of rapamycin (mTOR) is a serine/threonine kinase, which belongs to phosphatidylinositol-3 kinase (PI3K) related kinases family.[1] It regulates cellular metabolism, growth, and proliferation; and plays a major role in cancer metabolism.[2] Dysregulation of mTOR pathway occurs in several cancers conferring susceptibility to inhibitors. Rapamycin is the prototype for mTOR inhibitors and was initially evaluated by the Developmental Therapeutic Branch of the National Cancer Institute as antineoplastic agent. This has paved the path for further development of mTOR targeted therapies.[3] Temsirolimus and everolimus are the only two approved and commercially available mTOR inhibitors in the United States currently. Temsirolimus is approved for use in advanced renal cell carcinoma (RCC)[4] and everolimus is approved for advanced RCC,[5] subependymal giant-cell astrocytomas in tuberous sclerosis,[6] hormone receptor positive advanced breast cancer[7] and advanced pancreatic neuroendocrine tumors (NET).[8]

Commonly reported side effects with mTOR inhibitors include stomatitis, diarrhea, rash, fatigue, asthenia, metabolic complications, edema, infections and non-infectious pneumonitis.[9,10] Limited data is available on the incidence and relative risk (RR) of acute kidney injury (AKI) associated with mTOR inhibitor use. As per package insert, though dose modifications for renal failure are not recommended, renal toxicity and elevated creatinine are potential side effects of mTOR inhibitor use and require close monitoring. In a meta-analysis of treatment related mortality in patients receiving mTOR inhibitors for cancer, AKI was reported in four trials and was the second most common cause of fatal adverse events representing 5.7% of all study deaths.[11] Patients with RCC with impaired renal function are particularly at risk of developing AKI with everolimus use as shown in a retrospective analysis.[12] In order to systematically quantitate the RR and incidence of AKI in patients taking mTOR inhibitors, we attempted to conduct a trial level meta-analysis.

Methods of research

Selection of studies

An independent review of citations in English literature from PubMed/Medline from January 1966 to April 2019 was conducted. Key words included in the search were RCT, clinical trial, mTOR inhibitor, temsirolimus, torisel, everolimus, afinitor and cancer. Abstracts and virtual meeting presentations from major

conferences - American society of clinical oncology, European society of medical oncology (ESMO), and American association of cancer research (AACR) - were reviewed from January 2010 to April 2019. Updated manufacturer's package inserts and clinicaltrials.gov were also searched. Phase II and III RCTs comparing arms with and without an mTOR inhibitor were selected. Since the objective of this analysis was to quantify the differences in incidence of renal toxicity in the mTOR arm compared to non- mTOR arm, phase I trials, single-arm studies and studies which did not report any renal adverse events were excluded. Trials that contained an mTOR inhibitor in all arms were excluded. In case of duplicate publications, only the most recent and updated report of the clinical trial was included. Study quality was assessed by using the seven-point Jadad ranking system.[13]

Data extraction and primary end points

Data abstraction was conducted independently by two investigators (RG, RP) according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA-P) statement.[14] The variables extracted are shown in Table 1. The primary endpoints of the study included all and high-grade (grades 3-5) AKI and proteinuria based on Common Terminology Criteria for Adverse Events (CTCAE) version 3 or 4. Grades 1-5 AKI are defined as creatinine level increase of >0.3 mg/dL; creatinine 1.5-2.0 × above baseline, creatinine 2-3 × above baseline, creatinine >3 × baseline or >4.0 mg/dL; hospitalization indicated, life-threatening consequences; dialysis indicated and death respectively. Grade 1-3 proteinuria are defined as 1+ proteinuria: urinary protein <1.0 g/24 h, 2+ proteinuria: urinary protein 1.0-3.4 g/24 h and urinary protein ≥3.5 g/24 hours.

Statistical analysis

Statistical analyses were performed by using R statistical software, version 3.1.1.[15,16] The proportion and 95% confidence intervals (CIs) for patients with AKI were derived for each arm of each study and used to calculate the RR. The median therapy duration, where available, was used to estimate incidence rate ratios (IRR) for AKI. For studies reporting zero events in an arm, the classic half-integer correction was applied. Trials that either did not list AKI as an adverse event or reported no AKI in all arms were excluded.

For the meta-analysis, both the fixed-effects model and the random-effects model were considered; the method proposed by DerSimonian and Laird was used to estimate the random-effects model.[17] Statistical heterogeneity among studies included in the meta-analysis was assessed using the Cochrane's Q statistic, and inconsistency was measured using the I^2 statistic, which is used to describe the percentage of total variation across studies that is due to heterogeneity rather than chance; a value of 0% indicates no observed heterogeneity, while larger values between 0% and 100% show increasing heterogeneity.[18] The assumption of homogeneity was considered invalid for P-values <0.1, and in this case, we reported summary estimates from the random-effects models. Finally, potential publication bias was assessed using the Egger test for funnel plot asymmetry.[19,20] Two-tailed P-values <0.05 were considered statistically significant.

Results

Search results

Our search yielded 64 potentially relevant clinical trials with

Table 1. Characteristics of randomized trials included in the final analysis of the risk of renal toxicity with mTOR inhibitors.

Author, year	Phase	Histology	Patients enrolled (n)	Treatment arms	Evaluable patients per arm	Median age (yr) (range)	Median OS (95% CI) Months	Median PFS (95% CI) Months	Median therapy duration (range) Months	Acute kidney injury [all grade]	High grade (3/4)	Reported events	Jadad score
Baselga *et al.*, 2012	3	BRCA	724	Everolimus + exemestane Placebo + Exemestane	482 239	62 (34-93) 61 (28-90)	NR NR	10.6 (9.7-15) 4.1 (2.9-5.6)	6 3.3	1 0	1 (0.02%) 0	Renal failure, Increased creatinine	5
Motzer *et al.*, 2010	3	RCC	416	Everolimus + BSC Placebo + BSC	274 137	61 (27-85) 60 (29-79)	14.8 14.4	4.9 (4-5.5) 1.9 (1.8-1.9)	4.7 (0.63-15) 2 (0.7-6.5)	50 (18%) 34 (25%)	1 0	Increased creatinine	5
Bachelot *et al.*, 2012	2	BRCA	111	Everolimus + Tamoxifen Tamoxifen	54 57	63 (41-81) 66 (42-86)	NR 32.9	8.6 (5.9-13.9) 4.5 (3.6-8.7)	6.2 (0.7-31) 4.8 (0.7-27)	1 0	1	Renal failure	3
Hudes *et al.*, 2007	3	RCC	626	Temsirolimus Interferon alpha Temsirolimus + Interferon	208 200 208	58 (32-81) 60 (23-86) 59 (32-82)	10.9 (8.6-12.7) 7.3 (6.1-8.8) 8.4 (6.6-10.3)	5.5 (3.9-7) 3.1 (2.2-3.8) 4.7 (3.9-5.8)	3.8 (3.5-3.9) 1.9 (1.9-2.2) 2.5 (1.9-3.6)	35(17%) 24 (12%) 47 (23%)	7 (3%) 2 (1%) 7 (3%)	Increased creatinine	3
Negrier *et al.*, 2011	2	RCC	171	Temsirolimus + Bevacizumab Sunitinib Interferon alpha + Bevacizumab	88 42 40	62 (33-83) 61.2 (33-83) 61.9 (40-79)	NR NR NR	8.2 (7-9.6) 8.2 (5.5-11.7) 16.8 (6-26)	5.1 (0-12) 10.4 (0.5-12) 7.2 (1-12)	36 (41%) 2 (5%) 10 (25%)		Proteinuria Proteinuria Proteinuria	3
Rini *et al.*, 2014	3	RCC	791	Temsirolimus + Bevacizumab Interferon alpha + Bevacizumab	400 391	58.6 58.2	25.8 (21.1-30.7) 25.5 (22.4-30.8)	9.1 (8.1-10.2) 9.3 (9.0-11.2)	Not mentioned Not mentioned	141 (36%) 106 (27%)	64 (16%) 52 (13%)	Proteinuria	3
Yao *et al.*, 2013	3	Carcinoid	429	Everolimus + Octreotide Octreotide + placebo	215 211	60.1 59.4	NA NA	16.4 (13.67-21.19) 11.3 (8.44-14.59)	4.3 (1-41) 4.3 (1-40)	3 (1.40%) 1 (0.47%)		Acute renal failure	5
Yardley *et al.*, 2015	2	BRCA	113	Paclitaxel+ bevacizumab+Everolimus Paclitaxel+ bevacizumab+Placebo Placebo + BSC	56 57 184	61 (30-77) 57 (25-79) 64 (34-87)	17.5 (14.9-23.9) 19.6 (14.0-27.2) 7.3 (6.3-8.7)	9.1 (6.8-18.8) 7.1 (5.6-10.8) 2.6 (1.5-2.8)	6 m [1-37] 6 m [1-45] 8.9 (0.4-136)	13 (24%) 8 (14%)	4 (7%) 2 (4%)	Proteinuria	4
Choueiri *et al.*, 2015	3	RCC	658	Everolimus Cabozantinib	328 330	61 (31-84) 62 (36-83)	NA NA	3.8 (3.7-5.4) 7.4 (6.3-7.6)	NA NA	35 (11%) 15 (5%)	0 1 (<1)	Increased creatinine	5

BSC, best supportive care; CR, complete response; OS, overall survival; PFS, progression free survival; HCC, hepatocellular carcinoma; BRCA, breast cancer; PNET, pancreatic neuroendocrine tumor; NR, not reached; NA, not available; RCC, renal cell carcinoma.

mTOR inhibitor in cancer patients. After excluding phase I trials, trials with duplicate publications and trials not reporting renal toxicity as an adverse event in any of the arms, nine trials were considered highly relevant for the meta-analysis based on Jadad Scoring (Table 1). The selection process is shown in Figure 1s.

The trials enrolled patients with RCC (n=5), breast cancer (n=3) and NET (n=1). When examining by agent, temsirolimus was investigated in 3 trials and everolimus in 6. Temsirolimus was administered at a dose of 25 mg weekly except in one trial where it was administered at 15 mg weekly along with interferon in one of the arms. Dose of everolimus was 10 mg daily in all the trials. Patients in control arm received either a placebo (n=5 or other agents as shown in Table 1. The process for selection of studies is described in Figure 1.

Trial quality

Randomized treatment allocation sequences were generated in all trials. Five trials were placebo controlled. All the trials were of high quality with Jadad score of 3 in four trials, 4 in one trial and 5 in four trials.

Population characteristics

A total of 4039 patients from nine studies were available for the meta-analysis, 2313 in the mTOR group and 1704 in the non-mTOR group.[4,21-29] Two of these studies did not report median therapy duration, so incidence rates could not be estimated for these studies.[27,28] For high-grade AKI analysis, seven studies were available totaling 3439 patients (2010 in mTOR and 1411 in non-mTOR arms).[4,21,23-25,27-29]

Relative risk of AKI

All grade AKI occurred in 362 of 2313 (15.65%) patients receiving mTORs. In the non-mTOR group, all grade AKI occurred in 200 of 1704 (11.74%) patients. Subjects in the mTOR group were at significantly higher risk of all grade AKI (RR=1.551, P=0.010, 95% CI: 1.113 to 2.162) (Figure 2). There was significant evidence of heterogeneity in the RR for the studies included in this analysis (Q=21.00, P=0.007, I^2=61.9%).

High grade AKI occurred in 85 of 2010 (4.23%) patients receiving mTORs. In the non-mTOR group, high grade AKI occurred in 57 of 1411 (4.04%) patients. There was no significant difference in the risk of AKI for the two groups (RR=1.288, P=0.118, 95% CI: 0.938 to 1.769) (Figure 3). There was no significant evidence of heterogeneity in the RR for the studies included in this analysis (Q=3.09, P>0.20, I^2=0%).

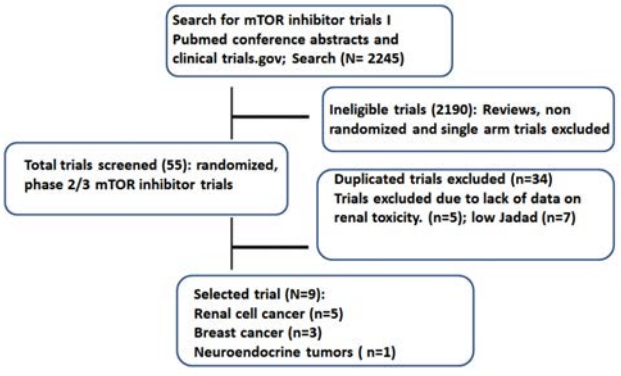

Figure 1. Selection process for the trials included in the meta-analysis.

Incidence rate ratio for AKI

For the seven studies for which incidence rates for all grade AKI could be estimated, there were 186 incidences of all grade AKI in 627.86 patient-years (IR=0.30 cases per patient-year) for the mTOR group and 79 incidences of all grade AKI in 307.53 patient-years (IR=0.26 cases per patient-year) for the non-mTOR group. There was no significant difference in incidence rates for the two groups (IRR=1.361, P>0.20, 95% CI: 0.536 to 3.616) (Figure 4). There was significant evidence of heterogeneity in the IRR (Q=51.53, P<0.001, I^2=88.4%).

For the six studies for which incidence rates for high grade AKI could be estimated, there were 21 incidences of high-grade AKI in 513.42 patient-years (IR=0.04 cases per patient-year) for the mTOR group and 4 incidences of high-grade AKI in 171.53 patient-years (IR=0.02 cases per patient-year) for the non-mTOR group. There was no significant difference in incidence rates for the two groups (IRR=0.818, P>0.20, 95% CI: 0.347 to 1.928) (Figure 5). There was significant evidence of heterogeneity in the IRR (Q=19.05, P<0.001, I^2=79.0%).

Publication bias

No evidence of publication bias was detected (P>0.20 using the Egger test).

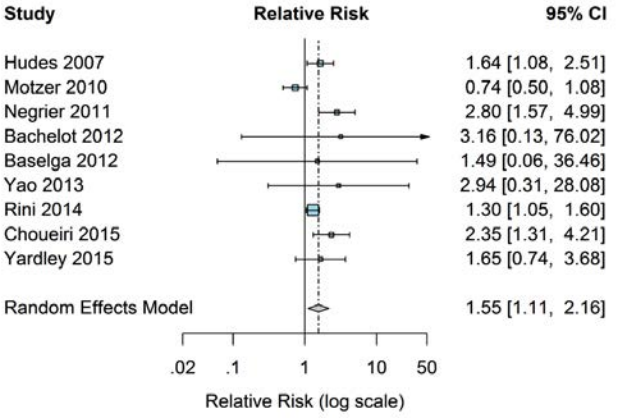

Figure 2. Risk ratio forest plot for all grades of AKI.

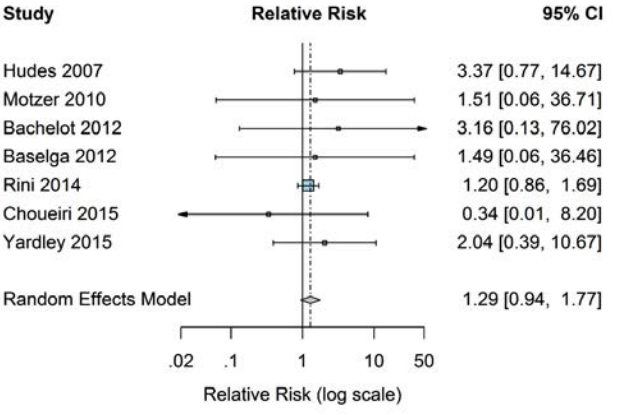

Figure 3. Risk ratio forest plot for severe grades of AKI.

Discussion

Drug induced nephrotoxicity is a commonly encountered clinical problem. It contributes to 66% of AKIs in hospitalized elderly patients[30] and is seen more often in patients with underlying renal dysfunction, cardiovascular disease or intra vascular volume depletion.[31] Pathophysiology of drug induced nephrotoxicity is diverse and includes mechanisms such as vasoconstriction, altered intraglomerular hemodynamics, interstitial nephritis, tubular cell toxicity, crystal deposition, thrombotic microangiopathy and osmotic nephrosis.[32] Often it is difficult to identify the medication that is causing AKI as patients may have underlying comorbidities and may be on multiple medications which might be contributing to it. In this meta-analysis, we attempted to quantitate the RR and incidence of AKI with mTOR inhibitor use. The mechanism of mTOR inhibitor induced nephrotoxicity is not completely understood. mTOR is activated after different forms of AKI and helps in regeneration and repair of renal tissue. Inhibition of mTOR delays recovery of renal function after AKI in animal models.[33] It was also shown in animal models that rapamycin delays renal recovery after AKI but does not prevent it. Recovery of renal function after AKI is likely due to the development of acquired tubular cell resistance to rapamycin.[34] Everolimus was shown to have antiproliferative effects and induces autophagy which aggravates tubular dysfunction during recovery from kidney injury.[35] Acute tubular necrosis was reported in four patients with mTOR inhibitor use with reversal of the renal function after discontinuation of the drug in two patients but the other two had chronic sequelae.[36] In a retrospective analysis of 18 Korean patients with non-dialysis dependent chronic renal failure and mRCC treated with mTOR inhibitors, elevation in creatinine was noted in 77% of the patients. Only one patient needed delay in treatment and dose reduction due to creatinine elevation and six patients required dose reduction due to non-renal toxicities. Efficacy and safety of mTOR inhibitor use was similar to patients with normal renal function.[37]

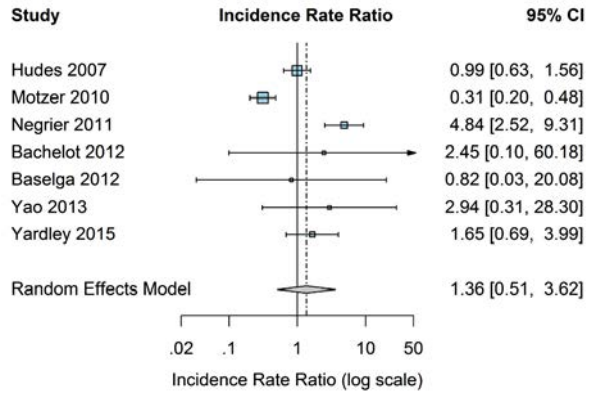

Figure 4. Incidence rate ratio forest plot for all grade AKI.

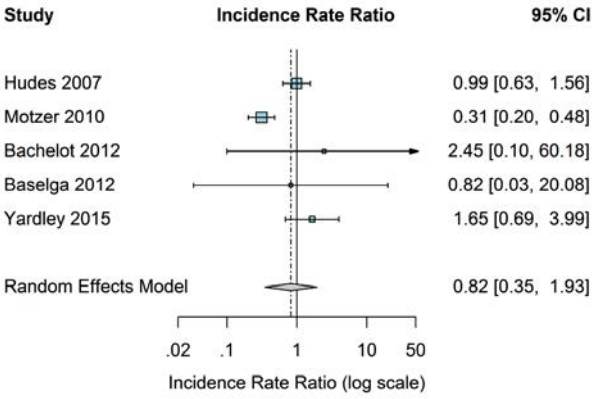

Figure 5. Incidence rate ratio forest plot for high grade AKI.

In this meta-analysis, we included randomized clinical trials of mTOR inhibitor use enrolling patients with a range of solid tumors. AKI as defined by elevation in creatinine and proteinuria per CTCAE were considered as primary end points for the analysis. The RR of all grade AKI in patients taking mTOR inhibitors compared to patients not on mTOR inhibitors was 1.55 (95% CI: 1.11 to 2.16, P=0.010). There was no significant difference in the risk of high-grade AKI for the two groups (RR=1.29, P=0.118, 95% CI: 0.94 to 1.77). Also, there was no significant difference in the incidence rates for either all grade or high-grade AKI between the two groups.

To our knowledge, this is the largest study addressing renal toxicity in patients taking mTOR inhibitors and included 4039 patients from nine studies. We included only phase II and III clinical trials comparing groups with and without an approved mTOR inhibitor. Phase I trials were not included as they are not randomized and include wide dose ranges. All the trials included were of high quality per Jadad system and there was no publication bias.

Our study has some limitations as with any other trial level meta-analysis. Patients analyzed may have underlying disease processes which itself might be causing renal failure, especially patients with RCC who have had nephrectomy and loss of renal mass have underlying renal dysfunction. Also, typically these patients are on multiple medications which can interact and increase the chances of AKI. For some trials, data is incomplete and updated information is not available. Some trials did not report adverse events occurring in <5-15% of patients. Unreported or missing data might bias our results. Also, since majority of the trials included in the meta-analysis are in RCC, some of the patients may have had underlying renal dysfunction which increases the risk of AKI and some trials may have attributed the AKI to underlying malignancy rather than as side effect of the medication. However, meta-analyses are considered reasonable to study rare events that are difficult to study in prospective studies. Our literature search included only articles published in English language which might have created some selection bias. The incidence of life-threatening AKI with the use of mTOR inhibitors is small, but can lead to long term complications like progression to chronic renal failure, dialysis dependence and death if severe. Patients should be thoroughly worked up for other causes of AKI before attributing it to mTOR inhibitor use. In conclusion, renal toxicity is a potential complication of mTOR inhibitor use and patients taking these medications should be closely monitored to prevent long term sequelae.

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