Emergent toxicities associated with the use of mTOR inhibitors in patients with advanced renal carcinoma

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The inhibitors of the mammalian target of rapamycin (mTOR) improve outcomes in patients with advanced renal cell carcinoma. These agents are associated with unusual class-adverse events that represent a challenge to the clinician, making it critical to recognize and treat them appropriately. This study aims to highlight the clinical management of these toxicities by presenting evidence from the literature and suggesting treatment recommendations. A critical review of the literature is performed and a summary of the most relevant emergent toxicities and their management is presented. Treatment recommendations of metabolic disturbances induced by mTOR inhibitors, such as hypophosphatemia, hyperglycemia, and hyperlipidemia along with the management of drug-induced pneumonitis and possible pharmacological interactions are presented. Most of these toxicities, if recognized and treated accordingly, should resolve with minimal impact on patients' quality of life and in the efficacy of this anticancer therapy. Oncologists should be familiar with the recognition and appropriate medical management of these clinical scenarios.

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Introduction

The phosphatidylinositol-3-kinase/AKT/mammalian target of rapamycin (mTOR) intracellular signaling cascade (Fig. 1) is critical in the control of cellular growth, proliferation, and survival [1]. Deregulation of this transduction pathway may contribute to a large fraction of human neoplasms [2]. Thus, elements of this cascade have emerged as potential targets for cancer therapeutics [3]. mTOR is an important target for the treatment of advanced renal cell carcinoma (RCC) and over the last 10 years, different mTOR inhibitors, such as temsirolimus, everolimus, and ridaforolimus (formerly known as deforolimus), have been developed and incorporated into clinical practice [4–7]. Therefore, the use of this type of agents is becoming widespread in the oncology community and physicians involved in the treatment of RCC should be familiarized with their common side effects and their appropriate management.

The development of new therapies for the treatment of advanced RCC has generated some interest in reviewing this topic and other investigators have published comprehensive publications [8,9]. In this study we describe those specific toxicities of mTOR inhibitors that merit special attention because of their novelty and/or particular treatment, and we provide management recommendations based on international guidelines and critical review of the available literature.

mTOR inhibitors in the clinical setting

Temsirolimus

Temsirolimus (sirolimus 42-ester 2,2-bis hydroxymethyl propionic acid; CCI-779: Torisel. Wyeth Pharmaceuticals, Madison, New Jersey, USA) is a water-soluble ester derivative of its parent compound, sirolimus, selected for development as an anticancer agent based on its more favorable pharmaceutical characteristics and superior therapeutic index in preclinical studies. Temsirolimus is rapidly metabolized through de-esterification to sirolimus, and both compounds bind to FKBP12 (FK506-binding protein) to exert anticancer activity in mTOR blockade. At several nontoxic doses temsirolimus showed antitumor activity alone or in combination with cytotoxic agents in a variety of human cancers [10–13]. In phase I studies rash and mucositis were dose-limiting, and other adverse events observed include eczematous reactions, dry skin, herpes-type lesions, nail disorders, mild myelosupression, hypercholesterolemia, hypertriglyceridemia, reversible decreases in serum testosterone, and rare episodes of euphoria [14,15]. A phase III clinical trial that randomized patients with poor prognosis advanced RCC to receive temsirolimus (25 mg IV over 30 min), or interferon-α or the combination of both (Global ARCC study) confirmed the superiority of temsirolimus over the other two arms and led to its approval. Major toxicity findings of this study revealed asthenia, rash and anemia

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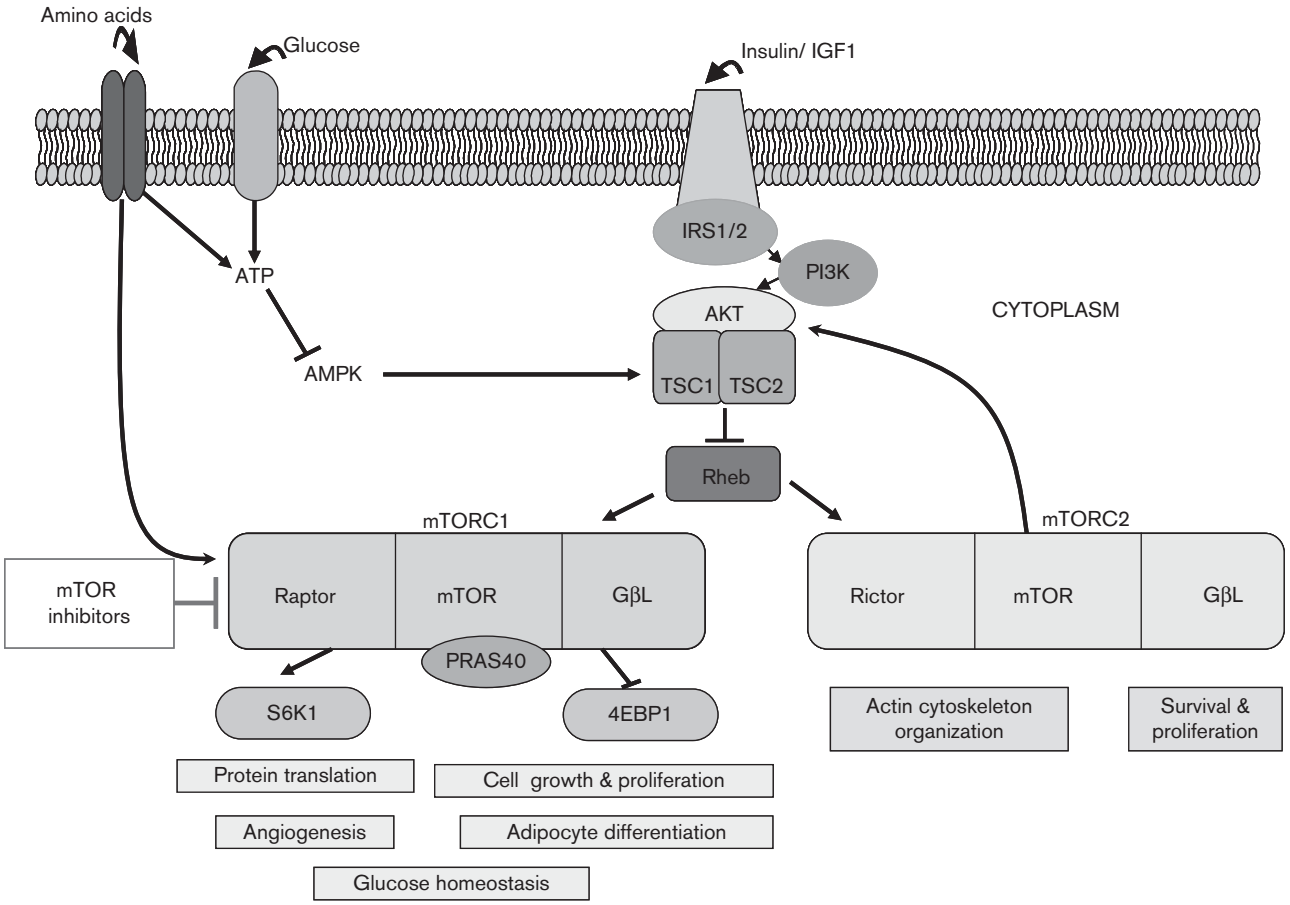
Fig. 1



The mammalian target of rapamycin (mTOR) pathway. mTOR is comprised of two different complexes mTORC1 (rapamycin-sensitive) and mTORC2 (rapamycin-resistant). The former integrates signaling to regulate S6K1 and 4EBP1 therefore controlling transcription, mRNA translation and metabolism. The latter participates in cytoskeleton organization and through AKT activates survival and proliferation.

as the most common side effects with 51, 47, and 45%, respectively. A significant percentage of patients presented with metabolic disturbances such as hyperlipidemia (27%), hyperglycemia (26%), and hypercholesterolemia (24%). Respiratory symptoms such as cough and dyspnea were reported in approximately a quarter of the patients (26 and 28% respectively) and stomatitis of different severities was observed in about 20%. However, the only adverse events that reached grade III–IV in more than 10% of the patients were anemia, asthenia and hyperglycemia [5]. Further studies have shown the relevance of other toxicities such as drug-related pneumonitis (DRP) that were underestimated initially [16,17]. One such study, a recently reported blinded radiological analysis of the Global ARCC study, revealed DRP in up to 29% of the patients who received temsirolimus versus 6% in the interferon arm [18].

Everolimus

RAD001, or everolimus (Afinitor; Novartis, Basel, Switzerland), is an oral sirolimus derivative compound with similar in-vivo activity and a superior pharmacokinetic profile than its parent compound. The main toxicities reported in early clinical trials include hypercholesterolemia, hypertriglyceridemia, mild leukocytopenia and thrombocytopenia [19]. A phase I trial concluded that 10 mg daily or 50 mg weekly were the recommended phase II doses, with stomatitis, neutropenia, and hyperglycemia being dose-limiting. Other toxicities included rash, fatigue, headache, anorexia, hypercholesterolemia, and hyperglycemia [19,20]. A phase III double-blind, placebo-controlled trial conducted on patients with advanced RCC, whose disease had progressed despite treatment with sunitinib and/or sorafenib, showed that everolimus (10 mg once daily) prolonged progression-free survival relative to placebo, leading to its recent approval by FDA [7]. In this trial the adverse events in the everolimus arm were mostly grade I and grade II. Stomatitis, rash, fatigue, and diarrhea were most frequently reported. Patients receiving everolimus had higher rates of grade III/IV stomatitis and infectious and noninfectious pneumonitis, than those in the

placebo arm. Hematologic adverse events such as grade III or IV lymphopenia and metabolic toxicities such as grade III hyperglycemia, hypophosphatemia, and hypercholesterolemia occurred more often in patients who were being treated with everolimus [7].

Ridaforolimus

AP23573, or ridaforolimus, is a phosphorus-containing analog of sirolimus. Preclinical and clinical data have shown anticancer activity of this compound either as monotherapy or in combination with cytotoxic or targeted agents [21,22]. Grade III mucositis was dose-limiting in a phase I trial in which AP23573 was given daily intravenously (i.v.) for 5 days every 2 weeks. Other side effects were mild-to-moderate and were consistent with those seen in this class of drugs, such as fatigue, nausea, rash, anemia, neutropenia, diarrhea, hyperlipidemia, and thrombocytopenia [23]. Antitumoral activity was observed in renal cell cancer patients. The dose of 12.5 mg per day, once daily for 5 consecutive days every 2 weeks (QDx5) in a 28-day cycle is being evaluated in phase II and III trials. Other schedules using weekly administration have also been tested and the recommended phase II is 75 mg as a flat dose, and again mucositis has been dose-limiting [4].

Medical management of selected toxicities

Hyperglycemia

Evidence from studies conducted earlier

Treatment with mTOR inhibitors increases blood glucose levels in both diabetic and non-diabetic patients. Approximately a quarter of the patients treated in the temsirolimus pivotal trial experienced different degrees of hyperglycemia and 11% were grade III–IV [5]. In the everolimus trial the numbers were overall higher with up to 50% of the patients presenting any grade of abnormally high glucose but only 12% of which were grade III and none were grade IV [7]. This is a drug class effect resulting from the mechanism of action of this family of compounds.

Management recommendations

It has been observed that patients who present with significantly higher glucose levels at baseline are more likely to develop treatment-related hyperglycemia. Therefore, it is recommended to reach good glycemic control before starting an mTOR inhibitor and to monitor closely the glucose levels in this patient population along with a comprehensive medical education allowing patients to recognize signs and symptoms typical of hyperglycemia.

The management of mTOR inhibitors-induced hyperglycemia is similar to that of diabetes of other causes, with oral hypoglycemic agents and/or insulin therapy according to standard guidelines and, if possible, under the supervision of an endocrinologist.

Evidence from guidelines

The International Diabetes Federation and the American Diabetes Association recently elaborated some systematic recommendations for the clinical management of this condition. First, it is necessary to be familiar with the criteria for diagnosis of diabetes involving any of the following: (i) symptoms of diabetes and casual plasma glucose lesser than 200 mg/dl (11.1 mmol/l). (The classic symptoms of diabetes include polyuria, polydipsia, and unexplained weight loss. Casual is defined as any time of day without regard to time since last meal). (ii) Fasting plasma glucose more than 126 mg/dl (7.0 mmol/l). (Fasting is defined as no caloric intake for at least 8 h.) (iii) Two hours plasma glucose more than 200 mg/dl (11.1 mmol/l) during an oral glucose tolerance test. The United Kingdom Prospective Diabetes Study established the importance of glucose control in prevention of vascular complications in people with type 2 diabetes. Epidemiological evidence shows a relationship between HbA1C and development of cardiovascular (CV) disease [24].

Guidelines recommendations

The American Diabetes Association recommends checking HbA1C in diabetics every 3 months until it is less than 7% and then at least every 6 months.

Life style and nutrition: Evidence supports the effectiveness of nutrition therapy and physical activity in the prevention and management of this metabolic disturbance [25].

Oral glucose-lowering drugs: A number of systematic evidence-based reviews addressing oral glucose-lowering drugs have been published in recent years confirming their effectiveness in protection against vascular complications. The evidence on better prevention of arterial outcomes when using metformin in the overweight substudy of United Kingdom Prospective Diabetes Study supports its primary use in overweight patients with type 2 diabetes and indeed, likely in the overall patient population with this disease [26].

Insulin therapy: There exists supporting evidence for the use of insulin in combination with metformin, insulin secretagogues (sulfonylureas), metformin and sulfonylureas (no meta-analysis), or thiazolidinediones in patients with type 2 diabetes [27].

Practical recommendations:

(1) Good glycemic balance before starting treatment.
(2) Close monitoring of the glucose levels.
(3) Good medical education so the patients can recognize signs and symptoms typical of hyperglycemia.
(4) Use of oral antidiabetics according to the recommendations summarized in the algorithm. Metformin (850 mg twice daily or three times daily) is the first option unless there is renal failure (creatinine clearance < 60 ml/min). If so, rosiglitazone (4 mg daily) is the alternative.

The following algorithm (Fig. 2) summarizes treatment recommendations for hyperglycemia in patients treated with mTOR inhibitors.

Hyperlipidemia

Another class-effect of m-TOR inhibitors comprises abnormalities in lipid metabolism including both hypertriglyceridemia and hypercholesterolemia.

Hypertriglyceridemia

The presence of hypertriglyceridemia has been associated with atherosclerosis, even in the absence of high levels of cholesterol and it can also lead to pancreatitis in excessive concentration. Very high triglyceride levels may also interfere with blood test resulting in false hyponatremia.

Evidence from studies conducted earlier

In the two major studies of temsirolimus and everolimus this side effect was observed in 27 and 71% of the patients respectively, although less than 4% of the cases reached grade III or greater [5,7]. These findings highlight the need to assess triglyceride levels before the start of treatment and the need to monitor their values during the course of therapy.

Hypercholesterolemia

Evidence from studies conducted earlier

The presence of abnormally high levels of cholesterol is also a common toxicity of both temsirolimus and everolimus. The frequencies reported in pivotal studies are similar to those of hypertriglyceridemia occurring in approximately a quarter of patients in the temsirolimus trial and 76% in the everolimus versus placebo trial. Again, these toxicities are generally grade I–II with scarce reports of toxicities $\geq$ grade III. This metabolic derangement contributes to many disease states, most notably cardiovascular (CV) disease (coronary artery disease, strokes, peripheral vascular disease, etc). Elevated cholesterol does not lead to specific symptoms unless it has been longstanding; but some types of hypercholesterolemia lead to specific physical findings (xanthoma, xantelasma palpebrum, arcus senilis).

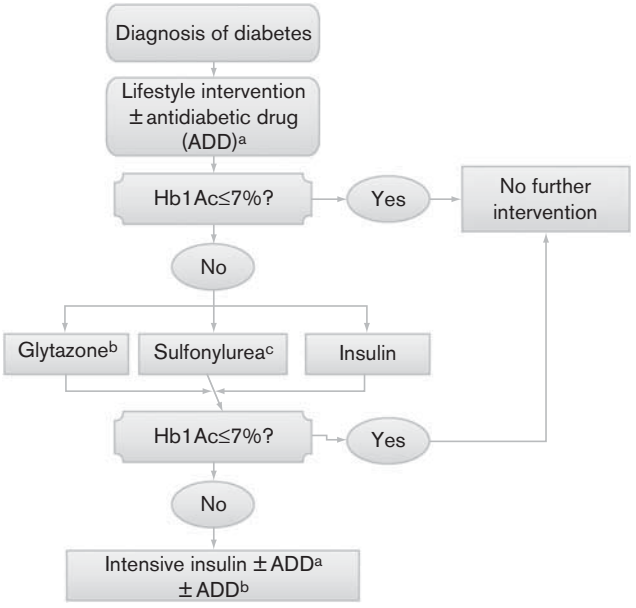
Management recommendations

Various clinical practice guidelines such as the American College of Physicians and the National Cholesterol Education Program have addressed the treatment of hyperlipidemia [28,29]. These guidelines take into account a series of risk factors and estimate the probability of a CV event over a period of years and provide recommendations accordingly. However, the clinical management of hypercholesterolemia and hypertriglyceridemia in patients with advanced RCC represents a different challenge given the context of a limited life expectancy. No definitive guidelines have yet been established for this patient population.

Practical recommendations

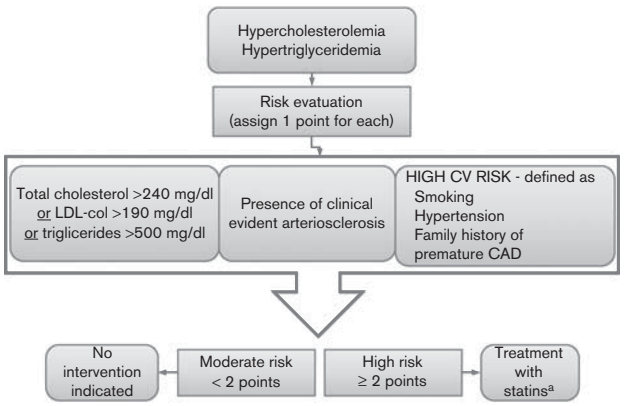
Our recommendations are to stratify patients based on CV risk factors ± earlier history of coronary artery disease and treat accordingly to the suggestions in Fig. 3. When active therapy is recommended, considering efficacy and toxicity profile, the HMGCoA inhibitors (i.e. statins) are the preferred option. If there exists any contraindication

Fig. 2



Algorithm proposed for the management of hyperglycemia in patients treated with mammalian target of rapamycin inhibitors. [a]Metformin 850 mg twice daily or three times daily, unless creatinine clearance less than 60 ml/min. If so, use rosiglitazone. [b]Rosiglitazone 4 mg daily. [c]Glibenclamide (also known as glyburide) start with 2.5 daily (it can be increased up to 15 mg/24 h).

Fig. 3



Algorithm proposed for the management of hyperlipidemia. CAD, coronary artery disease; CV, cardiovascular. [a]We recommend the use of atorvastatin at a dose of 10–20 mg daily. It does not require dose adjustment in combination with mammalian target of rapamycin inhibitors.

(such as elevation on liver enzymes greater than three times upper limit of normal) or intolerance to this group of drugs, other options such as bile acid sequestrants (i.e. colestipol) or cholesterol absorption inhibitors (i.e. ezetimibe) are valid alternatives.

Hypophosphatemia

Serum phosphate in adults normally ranges from 2.5 to 4.5 mg/dl (0.81–1.45 mmol/l). Hypophosphatemia is defined as mild (2–2.5 mg/dl, or 0.65–0.81 mmol/l), moderate (1–2 mg/dl, or 0.32–0.65 mmol/l), or severe (< 1 mg/dl, or 0.32 mmol/l).

Evidence from studies conducted earlier

This toxicity, with an unknown mechanism so far, is becoming more frequent in the era of molecularly targeted agents (i.e. tyrosine kinase inhibitors and mTOR inhibitors). Up to 32% of the patients treated with everolimus presented different degrees of low phosphate and 4% had grade III–IV hypophosphatemia [7].

The most common clinical manifestation of phosphate deficiency is weakness of skeletal or smooth muscles most of the times referred initially by the patient as fatigue. Any muscle group can be involved ranging from ophthalmoplegia to proximal myopathy to dysphagia or ileus. Through ATP depletion, and the consequent inability of muscle cells to maintain membrane integrity, hypophosphatemia can also cause rhabdomyolisis. Phosphate deficiency also impairs neurologic function, with different clinical scenarios that include confusion, seizures, and coma. Impaired cardiac contractility occurs in moderate-to-severe cases leading to generalized signs of myocardial depression and a reduced threshold for ventricular arrhythmias. Hemolytic anemia because of the inability of erythrocytes to maintain integrity of cell membranes in the face of ATP depletion, leading to their destruction in the spleen, has been associated with severe hypophosphatemia. Phosphate deficiency also compromises oxygen delivery to the tissues because of decreases in erythrocyte 2,3-DPG. Diminished oxygen delivery to the brain may be the cause of some of the neurologic manifestations mentioned before.

Management recommendations

It is necessary to rule out medical conditions such as hyperaldosteronism, chronic treatment with antiacids (aluminum salts), vitamin D deficiency and nutrition abnormalities that may be related with low phosphate levels. The recommended management of this toxicity is as follows:

Mild: Mild hypophosphatemia is generally asymptomatic and is not accompanied by long-term complications.

(1) Treatment: Oral phosphate supplementation with 1000–2000 mg phosphate element divided in 3–4 doses per day.
(2) Monitoring: Monthly monitoring of serum phosphate is appropriate.
(3) Dose adjustment: No change in the dose of mTOR inhibitor is required as this toxicity is easily managed with oral supplementation.

Moderate hypophosphatemia:

(1) Treatment: Oral phosphate supplementation with 1000–2000 mg phosphate element divided in 3–4 doses per day.
(2) Monitoring: Weekly monitoring of serum phosphate.
(3) Dose adjustment: No change in the dose of mTOR inhibitor is required as this toxicity is easily managed with oral supplementation.

Severe hypophosphatemia: It can present as severe organ dysfunction.

(1) Treatment: The patient would need admission and i.v. phosphate replacement.
(2) Monitoring: Daily monitoring of phosphate, calcium, and magnesium.
(3) Dose adjustment: Definitive interruption of the mTOR inhibitor and consider alternative anticancer agents when the toxicity is recovered.

Interstitial lung disease

Evidence from studies conducted earlier

Nonspecific interstitial pneumonitis is another potential toxicity associated with the use of mTOR inhibitors. We already reported our experience in two cohorts of patients with endometrial and neuroendocrine tumors treated with weekly doses of temsirolimus. Up to 36% of DRP was observed although 50% of them were asymptomatic and did not require any intervention [16]. However, in the first randomized studies conducted in advanced RCC with mTOR inhibitors, this phenomenon was likely underestimated. Pulmonary toxicity was initially reported in the form of cough in 26% of patients in the temsirolimus arm versus 15% on interferon ($P = 0.0006$) in the global ARCC study [5]. More recently, Maroto *et al.* [18] presented data from a blinded, independent, retrospective radiological review of the same study reporting DRP, as identified by radiographic changes on chest CT images, in 29% (52 out of 178) of patients with poor–prognosis-advanced RCC who were treated with temsirolimus and were evaluable for radiological changes. However, only 52% of these patients were symptomatic. Onset of DRP occurred within the first 8 weeks in the majority of the patients (60%); the most common radiographic findings were ground glass opacities (71%) and consolidation (62%), and cough and dyspnea were the most common symptoms at presentation. Similar data have also emerged from the everolimus studies. Motzer *et al.* [7] initially reported an 8% incidence of DRP in patients treated with this compound and again, more recent reports have shown that the incidence of this

phenomenon in patients receiving everolimus is higher than reported earlier and that patients should be monitored closely if radiological changes suggesting DRP develop [30].

Practical recommendations

We present the following recommendations for management (Fig. 4):

Pulmonary function tests (PFT): All patients to be treated with mTOR inhibitors should have baseline PFT including DLCO determination. This parameter has been shown to be the most sensitive for detecting pulmonary damage in the context of DRP [16].

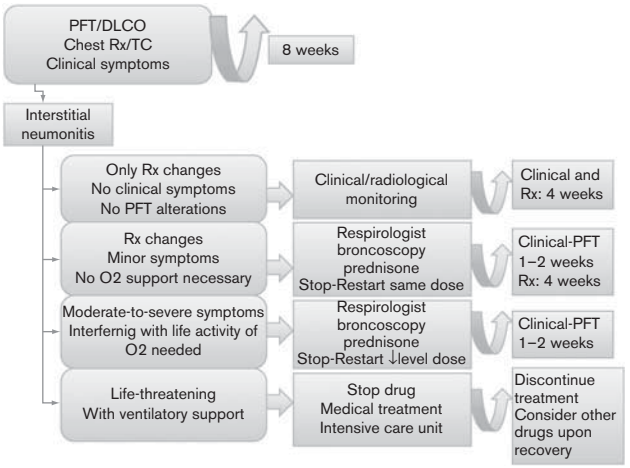
Imaging tests: Regardless of the location of metastatic disease all patients with advanced RCC treated with an mTOR inhibitor should have regular chest CT (every 8–12 weeks) to monitor the possible development of pulmonary changes. Ground-glass opacities and lung consolidations are the most typical changes observed in DRP.

Clinical symptoms: Patients should be monitored for cough and/or dyspnea, especially during the first 8 weeks of treatment. The clinician must be aware of the differential diagnosis of pneumonitis to rule out other nontreatment-related causes.

When DRP is confirmed, the first approach would be to grade its level of severity and then proceed according to the following suggestions:

(1) Grade I: Defined as radiological changes only.
   (a) Treatment: No specific treatment.
   (b) Medical management: Chest CT scan and PFT with DLCO should be performed at presentation and every 4–8 weeks to monitor progression.
   (c) Dose adjustment: No mTOR inhibitor dose adjustment is required.
(2) Grade II: Defined as a patient who has some symptoms that do not interfere with daily activities and no oxygen support is indicated.
   (a) Treatment: No specific treatment is needed.
   (b) Medical management: Chest CT scan and PFT (including DLCO), a respirologist consult, consideration of bronchoscopy with BAL, and a closer clinical monitoring with bi-weekly clinical controls and monthly chest imaging. If any decline in clinical status occurs, treatment should be held, a microbiological etiology ruled out, and the patient started on prednisone at a dose of 1 mg/kg.
   (c) Dose adjustment: If treatment had to be held, on resolution of the symptoms, the mTOR inhibitor can be restarted at the same dose or one dose level below at the physician's discretion.
(3) Grade III: Defined as symptomatic and interfering with daily activities and/or requiring O2.
   (a) Treatment: Hold the mTOR inhibitor.
   (b) Medical management: The patient should be referred to a respirologist to perform a complete study including PFS (DLCO), chest CT scan, bronchoscopy with BAL ± biopsy. An infectious etiology should be ruled out and the patient should be started on prednisone at a dose of 1 mg/kg.
   (c) Dose adjustment: On the resolution of symptoms, the mTOR inhibitor should be restarted at one dose level below if clinically indicated.
(4) Grade IV: Defined as life threatening with ventilatory support indicated.
   (a) Treatment: Hold the mTOR inhibitor.
   (b) Medical management: Admit the patient to an intermediate or intensive care unit to provide appropriate treatment. If clinically feasible complete study including PFS (DLCO), bronchoscopy with BAL ± biopsy should be completed. If an infectious etiology is ruled out, initiate prednisone at a dose of 1 mg/kg.
   (c) Dose adjustment: On the resolution of acute events, consider other therapeutic anticancer treatments Fig. 4.

Fig. 4



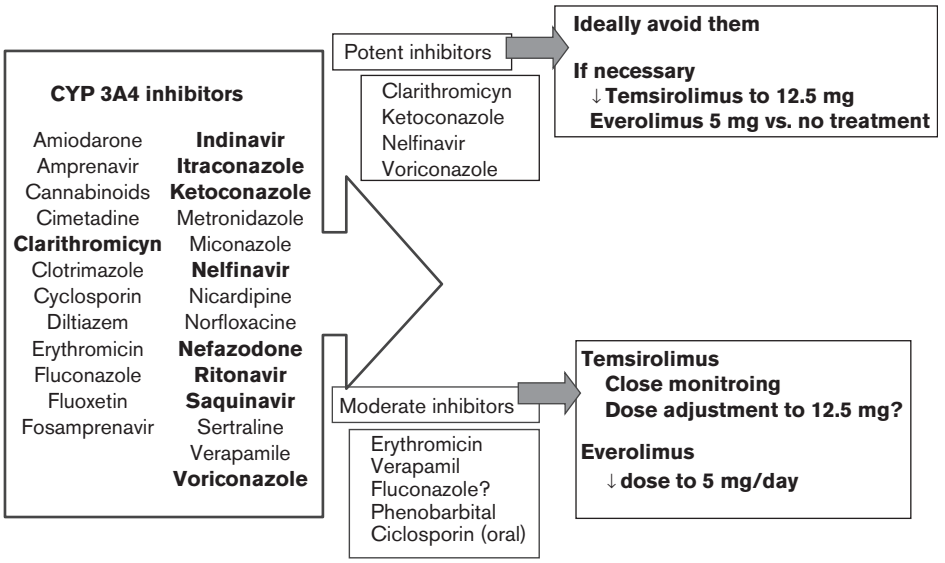
Algorithm proposed for the management of interstitial pneumonitis. DLCO, diffusing capacity of the lung for carbon monoxide; PFT, pulmonary function test – Spirometry.

Drug interactions

Effects of different drugs on mTor inhibitors

Inducers of cytochrome p450 (Fig. 5): Temsirolimus and sirolimus are metabolized by cytochrome *P*4503A4 (CYP3A4), a major isozyme in the liver known to participate in the metabolism of a significant number of compounds [31]. This enzyme is responsible for the formation of five temsirolimus metabolites. It has been shown that different rapamycin analogs, including tacrolimus, sirolimus, temsirolimus and everolimus, exhibit CYP3A-mediated drug interactions and several studies have evaluated the effect of concomitant CYP3A inducers on the PK parameters of temsirolimus and sirolimus [32,33].

Fig. 5



CYP 3A4 inhibitors: management in combination with mammalian target of rapamycin inhibitors. Bolded are the strong inhibitors.

(1) Temsirolimus: A study reported by Boni *et al.* [33] analyzed the effect of CYP3A4A inducers in two groups of patients: (i) patients with different malignancies treated within an exploratory study with doses of temsirolimus of up to 220 mg; (ii) healthy participants treated with single doses of temsirolimus (i.v. and oral) and rifampin (a strong CYP3A4 inducer). It was observed that coadministration with enzyme inducers decreased temsirolimus maximum plasma concentration (C_{max}) by 36% and increased the volume of distribution by 99%. In the first group of patients, Sirolimus $C_{max,}$ and area under the concentration–time curve (AUC) were decreased by 67 and 43%, respectively. In the healthy adult participants, coadministration of 25 mg i.v. temsirolimus with rifampin had no significant effect on temsirolimus C_{max} and AUC but decreased sirolimus C_{max} and AUC by 65 and 56%, respectively. Thus, if agents with potent CYP3A induction potential must be used, an increase in temsirolimus dosage should be considered. A weekly dose of 50 mg would be the recommended adjustment to minimize the risk of subtherapeutic levels although there are no solid clinical data in this regard.

(2) Everolimus: Everolimus is a substrate of CYP3A4 too [34–37] and also a substrate and moderate inhibitor of PgP. Therefore, absorption and elimination of this drug may be influenced by other drugs that affect CYP3A4 and/or PgP. *In vitro*, everolimus is a competitive inhibitor of CYP3A4 and a mixed inhibitor of CYP2D6. Potent CYP3A4 inducers (i.e. rifampin) can decrease everolimus blood levels. If patients require coadministration of a potent CYP3A4 inducer, an everolimus dose increase from 10 mg daily up to 20 mg daily should be considered: 5 mg increases starting on day 4 and 8 following the start of the inducer agent [38].

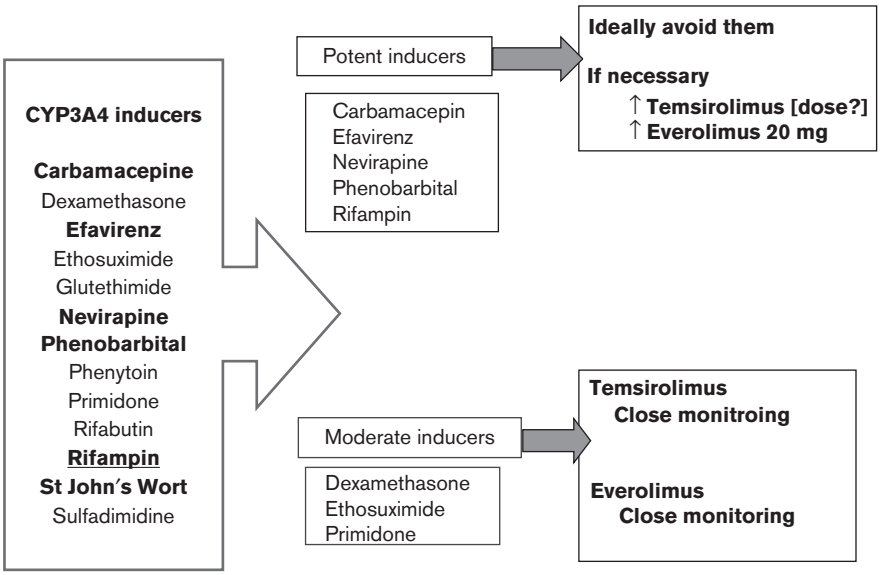
Inhibitors of cytochrome p450 (Fig. 6):

(1) Temsirolimus: Similar studies have been conducted regarding the effect of CYP3A inhibitors [32]. Concomitant use of strong CYP3A4 inhibitors (e.g. ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, grapefruit juice, and voriconazole) should be avoided in patients receiving weekly doses of 25 mg of i.v. temsirolimus. A reduction of the temsirolimus dose to 12.5 mg weekly should be considered if a concomitant strong CYP3A4 inhibitor agent is strictly necessary. When the inhibitor is discontinued, a washout period of approximately 1 week should be allowed before the temsirolimus dose is adjusted back to the dose used earlier.

(2) Everolimus: Potent CYP3A4 and/or PgP inhibitors (i.e. ketoconazole) may increase everolimus concentration, and concomitant treatment is thus not recommended. Moderate CYP3A4 and/or PgP inhibitors (i.e. verapamil or erythromycin) produce mild or moderate elevation in everolimus blood levels; some guidelines recommend a dose reduction to 5 mg daily, although there is a lack of definitive support for this in the literature.

(3) Effects of mTor inhibitors on other drugs: As mentioned earlier, it is known that temsirolimus and sirolimus are both substrates of CYP3A4, but neither is an inhibitor or inducer of CYP3A4. Thus,

Fig. 6



CYP 3A4 inducers: management in combination with mammalian target of rapamycin inhibitors. Bolded are the strong inducers.

the effect of i.v. temsirolimus administration on the metabolism of other CYP3A4 substrates should be minimal or negligible. These include glucose-lowering agents and HMG-Co A reductase inhibitors that may be necessary for the treatment of hyperglycemia and hyperlipidemia (both relatively common side effects related to mTOR inhibitors) and benzodiazepines (commonly used in cancer patients for anxiety). Although antifungal agents that are strong inhibitors of CYP3A4 (e.g. ketoconazole and itraconazole) should be avoided in patients receiving temsirolimus as addressed in the earlier paragraph, moderate CYP3A4 inhibitors (e.g. fluconazole and voriconazole) may not have as much interaction potential. Therefore, in RCC patients treated with 25 mg i.v. temsirolimus, fluconazole (commonly used for treatment of chemotherapy-induced mucositis) may be a reasonable agent to administer.

These recommendations are equally applicable to everolimus and ridaforolimus although the medical literature is more scarce and perhaps more caution should be applied when using inhibitors of CYP3A4 with everolimus [39] (Figs 5 and 6).

Conclusion

In recent years we have witnessed the birth and development of a variety of new molecularly targeted agents for the treatment of solid tumors and hematological malignancies. Many of these compounds use novel mechanisms of action and some of their side effects can be considered as 'unusual' in the field of oncology. A paradigmatic example is found in the mTOR inhibitors. Their toxicity profile is characterized by adverse events that clinical oncologists consider common and present no novelty in management, such as diarrhea, nausea or hematologic toxicities with comparable or even less severity than the ones observed with traditional cytotoxic therapies. However, mTOR inhibitors also exhibit other adverse events that can represent 'unusual toxicities' because of their rare presentation in relation to conventional cytotoxics: these are progressively becoming more frequent with the increased use of novel molecules in oncology. In this study we have aimed to highlight the clinical management of these toxicities by presenting evidence from the literature and suggesting our management recommendations. Some of these, the 'metabolic toxicities' for example, are well known to other specialists and their management is well established in nononcological populations. However, their treatment in oncology patients and particularly in those with advanced renal cancer is challenging as these patients have survivals in the range of months to few years whereas standard guidelines are based on probabilities of events on the general population with a much higher life expectancy. Thus, we proposed more flexible approaches in such populations that are greatly affected by short-term symptoms and/or complications.

Other toxicities such as mTOR inhibitors DRP and drug-related hypophosphatemia represent newer clinical challenges. Finally, we reviewed and made suggestions regarding the management of drug interactions and metabolism, aiming to illustrate the importance of being cognizant of the potential effects of certain drugs interactions.

Although mTOR inhibitors are agents that may effect significant benefit in cancer patients, they are associated with emergent toxicities that must be well-understood and managed appropriately by the medical oncologist. Appropriate management would translate into lower toxicity rates and avoid unnecessary early treatment delays or terminations that would negatively affect outcomes.

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