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Characterisation of the lung toxicity of the cell cycle inhibitor temsirolimus

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ABSTRACT

The aims of this study were reviewing our experience regarding the pulmonary toxicity of the mammalian target of rapamycin (mTOR) inhibitor temsirolimus, discussing potential pathogenic mechanisms and proposing management strategies. Medical records and radiological reports of 22 patients treated with weekly doses of temsirolimus 25 mg were reviewed. Eight (36%) out of 22 patients developed pulmonary abnormalities compatible with drug-induced pneumonitis. Half were asymptomatic and in those with symptoms, dyspnea and dry cough were the most common. Radiologically two different patterns, ground glass opacities and lung parenchymal consolidation, were described. The management of this toxicity was variable, ranging from no intervention to discontinuation of the drug. In our experience temsirolimus may cause drug-induced pneumonitis at a higher incidence than that previously reported. The presentation and its severity are variable. The risk of developing this toxicity may be increased among subjects with abnormal pretreatment pulmonary functions or history of lung disease.

1. Introduction

The mammalian target of rapamycin (mTOR) is a serine–threonine kinase that participates in the regulation of cell growth, proliferation and apoptosis through modulation of cell cycle progression.[1,2] mTOR modulates translation of key mRNAs of proteins required for cell cycle progression from G_1 to S phase, such as 4E-binding protein (4E-BP1) and $p70^{S6}$ kinase.[3] Rapamycin (sirolimus) and its derivatives are immunosuppressive macrolides that block mTOR and yield potential antiproliferative activity in a variety of malignancies.

Sirolimus, produced by *Streptomyces hygroscopicus*, binds intracellularly to the immunophilin FKBP-12 (FK 506-binding protein-12) creating a complex that inhibits the protein kinase activity of mTOR. Inhibition of mTOR prevents phosphorylation of $p70^{S6}$ kinase, 4E-BP1 and, indirectly, other proteins involved in transcription and cell cycle control, leading to G_1 growth arrest of lymphocytes. In addition to its immunosuppressive properties, sirolimus has been shown to exert potential anticancer effects through different mechanisms. These include interference with the proliferation of endothelial and vascular smooth muscle cells required for tumour angiogenesis, and induction of apoptosis, thereby

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sensitising cancer cells to DNA-damaging agents such as cisplatin. Furthermore, sirolimus inhibits the oncogenic transformation of human cells induced by either PI3K or PKB/Akt, and causes tumour growth inhibition in xenograft models.[4,5] Sirolimus has been increasingly used either alone or in combination with low doses of calcineurin inhibitors in patients following renal transplantation for prevention of allograft rejection. The main toxicity observed with sirolimus has been dose-dependent and consist primarily of hypercholesterolemia, hypertriglyceridemia and thrombocytopenia. Case series in the literature have reported on the rare occurrences of sirolimus-associated pulmonary toxicity in the form of diffuse interstitial pneumonitis.[6–9] In spite of its antiproliferative activity, the unfavourable pharmaceutical properties of sirolimus, such as poor aqueous solubility and instability, preclude its clinical development as an anticancer agent. Other sirolimus analogs with improved pharmacological profiles have thus been developed.

Clinical trials using three sirolimus derivatives have been performed, these include temsirolimus[10][CCI-779; Wyeth], everolimus[11] [RAD001; Novartis] and AP23573[12] [Ariad Pharmaceuticals]. The pharmacological action of these compounds, like sirolimus, is mediated through intracellular binding to FKBP-12 and subsequent inhibition of mTOR.[13]

Temsirolimus (sirolimus 42-ester 2,2-bis hydroxymethyl propionic-acid) is a more water-soluble ester derivative of sirolimus, selected for development as an anticancer agent based on its favourable pharmaceutical characteristics and superior therapeutic index in preclinical studies. At several non-toxic doses temsirolimus demonstrated antitumour activity alone or in combination with cytotoxic agents in a variety of human cancer models such as gliomas, rhabdomyosarcomas, head and neck, prostate, pancreatic and breast cancers.[10,14–17] Temsirolimus has already been tested in phase I and II trials with promising activity and good safety profile.[18–20] Different doses ranging from 0.75 to 250 mg/m^2 in either a daily or a weekly schedule have been used and pharmacokinetic (PK) studies have shown that temsirolimus C_{max} and AUC values increase in a less-than-proportional manner with increasing doses. However no difference in activity has been observed in higher versus lower doses with increased toxicity in the former. In phase I studies of temsirolimus 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. Pulmonary toxicity has been previously described in the clinical literature of temsirolimus.[20]

RAD001 or everolimus, is an oral sirolimus derivative compound with similar in vivo activity and a better pharmacokinetic profile than its parent compound. Its antineoplastic activity has been evaluated in different human cancer cell lines and in xenograft models with median inhibitory (IC_{50}) values in the range of 5–1800 nM. The main toxicities reported include hypercholesterolemia, hypertriglyceridemia, mild leukocytopenia and thrombocytopenia.[1] A recently reported phase I trial concluded 10 mg on a daily schedule and 50 mg on a weekly schedule as the recommended phase II doses, with stomatitis, neutropenia and hyperglycaemia being dose limiting.[1,11,21] Other toxicities included rash, fatigue, headache, anorexia and hypercholesterolemia.

AP23573 is a phosphorus-containing analog of sirolimus. Preclinical and clinical data have shown activity of this compound administered either as a single agent or in combination with cytotoxic or targeted agents.[22,23] Grade 3 mucositis has been dose-limiting in a phase I trial where AP23573 was given intravenously daily for 5 days every 2 weeks. Other side effects were mild to moderate and consistent with those seen with this class of drugs, such as fatigue, nausea, rash, anaemia, neutropenia, diarrhoea, hyperlipidemia and thrombocytopenia.[12]

Sirolimus and its derivatives constitute a family of antineoplastic drugs that possess acceptable toxicity profiles, with skin rashes and mucositis being dose-limiting. Pulmonary toxicity has been described with sirolimus and temsirolimus, but only scant information is published about the latter. Consistent clinical or radiological patterns have not been defined, and no pathogenic mechanisms have been proposed as potential causes of this visceral toxicity with temsirolimus. Furthermore, guidelines on the clinical management of this toxicity are needed. In this report, we present our experience with the pulmonary toxicity encountered in a subgroup of patients receiving weekly doses of temsirolimus on two clinical trials, along with a review of the literature on this topic, and a discussion about potential pathogenic mechanisms and management strategies.

2. Patients and methods

Medical records and radiological reports of patients who have been enrolled in two ongoing clinical trials of temsirolimus at the Princess Margaret Hospital were reviewed. One trial evaluated the efficacy of temsirolimus in patients with advanced neuroendocrine tumours (NET) and the other in patients with advanced endometrial carcinoma (EC). In both trials, patients received single-agent temsirolimus at 25 mg intravenously over 30 min on a weekly schedule and response was assessed with chest and abdominal-pelvic computer tomography (CT) scans every 8 weeks. All patients had baseline studies including a radiological chest evaluation. Chest X-rays and CT scans of all patients with abnormal findings on study were reviewed with an independent radiologist (T-B.C.). The conduct of both clinical trials was approved by the University Health Network Research Ethics Board.

3. Results

Twenty-two patients were treated in our institution with weekly doses of temsirolimus from January 2004 to March 2005 on two ongoing clinical trials, 15 patients had advanced NET and 7 patients had advanced EC. The median age was 55 (range 36–74), 68% were female, 12 patients had Eastern Cooperative Oncology Group (ECOG) performance status 0 and 10 patients had ECOG 1. Eighteen percent were current or ex-smokers, and 22% had a past medical history remarkable for pulmonary disease including chronic obstructive pulmonary disease (1 patient) and asthma (4 patients). Nine patients had previous chemotherapy regimens and 5 had received prior radiation. None of the patients had received any chest

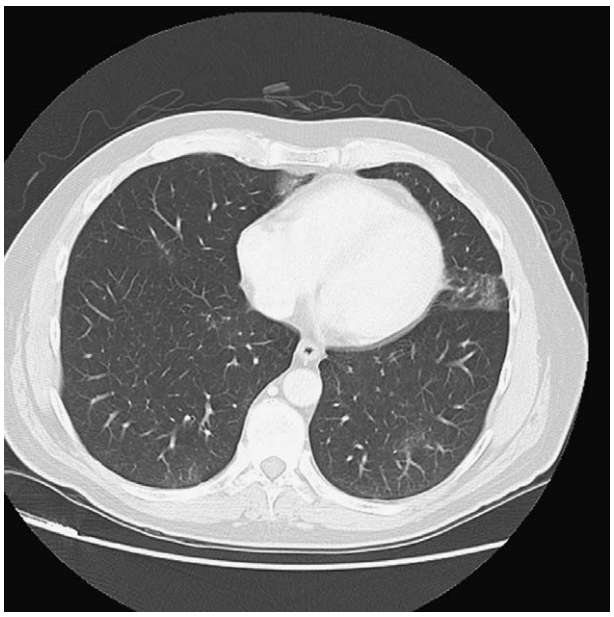

Fig. 1 – Thorax CT with GGO/DID pattern.

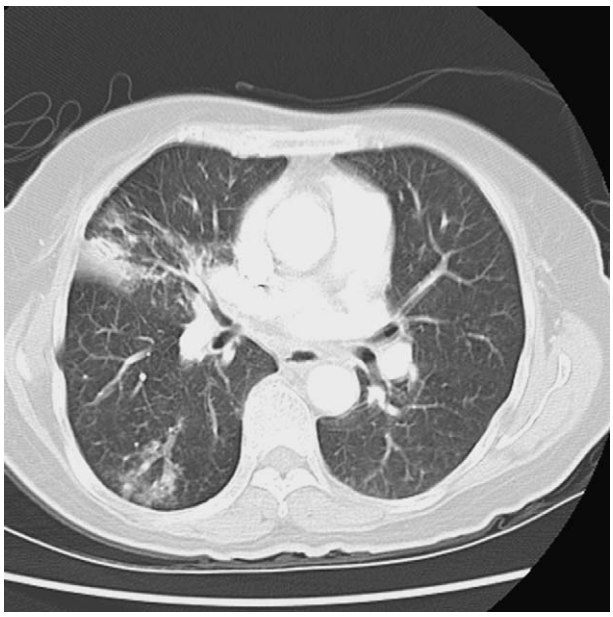

Fig. 2 – Thorax CT with LPC pattern.

irradiation within a pulmonary field. Thirteen patients were chemonaive.

Ten (45%) of the 22 patients developed pulmonary abnormalities on thoracic imaging tests performed (chest X-rays [1 patient] and CT scans of thorax [9 patients]) during their courses on study. These radiological abnormalities were associated with an extensive range of clinical scenarios. Upon independent review, these abnormalities were categorized into two different radiological patterns: (a) ground glass opacities (GGO) with or without diffuse interstitial disease (DID) (Fig. 1) and (b) lung parenchymal consolidation (LPC) (Fig. 2). After correlating the clinical data with the radiological findings, 2 patients within the LPC group, had clinical scenarios compatible with an acute pulmonary infection that resolved with conventional treatment. However, 8 patients (36%) were classified as experiencing possible drug-induced pneumonitis (DIP), due to the lack of evidence of other conditions to explain these radiological changes. Five of these patients (3 NET and 2 EC) presented findings compatible with the GGO/DID pattern and three (2 NET and 1 EC) were included in the LPC group (Tables 1 and 2). Out of these 8 patients, 6 were non-smokers, 1 was an ex-smoker and 1 was an active smoker.

All patients diagnosed with DIP were treated at the same schedule and dose of temsirolimus at 25 mg/week. Out of the 8, 4 were withdrawn from additional treatment (one due to the diagnosis of invasive aspergillosis, two due to simultaneous occurrences of DIP and progression of their malignancies and one due to disease progression while the DIP was not causing any symptoms). In 2 patients the treatment was interrupted temporarily (1 patient for 2 weeks; 1 patient for 3 weeks) due to radiological changes with little or no clinical symptoms. Pulmonary function tests (PFTs) performed on these 2 patients showed no abnormalities in one patient

Table 1 – Characteristics of patients included in the *ground glass opacities/diffuse interstitial disease* group

Patient	Primary	Onset	Symptoms	Pulmonary function tests	Radiological findings	Response to discontinuation of temsirolimus
1	Pancreas NET (Glucagonoma)	1.5 months	Dyspnea on exertion		Diffuse interstitial disease	Clinical and radiological improvement
2	EC	3.5 months	Asymptomatic	PFTs: ↓ DLCO	Diffuse multifocal ground-glass opacities	Radiological improvement
3	GI NET	3 months	Mild dry cough		Multifocal ground-glass opacities	Patient continued on temsirolimus
4	EC	3 months	Asymptomatic	PFTs: ↓ DLCO	Diffuse interstitial disease	Patient continued on temsirolimus
5	Pancreas NET (Islet cell tumour)	2.5 months	Dyspnea on exertion, dry cough and chest pain		Diffuse interstitial disease	Almost complete clearing of radiological abnormalities

NET: Neuroendocrine tumour; EC: Endometrial carcinoma; GI: Gastrointestinal; PFTs: Pulmonary function tests. DLCO: Diffusing lung capacity for carbon monoxide.

Table 2 – Characteristics of patients included in the *lung parenchyma consolidation* group

Patient	Primary	Onset	Symptoms	Pulmonary function tests and BAL culture results	Radiological findings	Response to discontinuation of temsirolimus
6	Pancreas NET	2 weeks	Cough, fever, eosinophilia	BAL culture: *Aspergillus fumigata* PFT: ↓ DLCO	CT[1]: Consolidation in RUL; CT[2]: Cavitation in RUL, consolidation in RML and RLL	Temsirolimus stopped definitively after 3 weeks; patient improved after receiving antifungal therapy (Itraconazole 100 mg bid)
7	EC	4 months	Asymptomatic	PFT: ↓ DLCO	Consolidation in RLL and LLL	No changes during drug interruption (2 weeks); patient continued on temsirolimus (25 mg)
8	GI NET	3 months	Asymptomatic	PFT: ↓ DLCO BAL culture: *Aspergillus fumigata*	Consolidation in RML and RLL	No changes during drug interruption (2 weeks); patient continued on temsirolimus (25 mg)

NET: Neuroendocrine tumour; EC: Endometrial carcinoma;GI: Gastrointestinal; DLCO: Diffusing lung capacity for carbon monoxide; BAL: Broncho-alveolar lavage;PFTs: Pulmonary function tests. RUL: Right upper lobe of lung; RML: Right middle lobe of lung; RLL: Right lower lobe of lung; LLL: Left lower lobe of lung.

and a mildly reduced diffusing capacity for carbon monoxide (DLCO) in the other. Neither of them received any specific therapy for their abnormal radiological findings. Due to stability in their clinical status and PFTs, temsirolimus was reintroduced. In one patient an additional cycle was given and then stopped due to other toxicities. The other patient was restarted on temsirolimus and remains currently on study beyond 10 cycles. The remaining 2 patients with DIP had little or no symptoms and thus continued on temsirolimus without interruption in spite of radiological abnormalities that remained stable along their study course.

Dose reduction was not used as an option to manage this toxicity in our series. The onset of the DIP was variable but always within the first 16 weeks after treatment start (median 12; range: 2–16 weeks). Dose discontinuation led to resolution of radiological abnormalities in all the patients. Fifty percent of the patients in our series were asymptomatic and in those who presented with symptoms, dyspnea and dry cough were the most common. Interestingly 2 of the patients included under the LPC category (patients #6 and #8) were diagnosed with different presentations of aspergillosis during their temsirolimus therapy, with no analytical evidence of immunosupression (i.e. no neutropenia, no lymphopenia).

4. Discussion

Rapamycin and its derivatives (temsirolimus, everolimus, and AP 23573) constitute a family of immunosuppressive and antineoplastic drugs that possess acceptable toxicity profiles. Skin rashes and mucositis have been described as dose-limiting. Pulmonary toxicity has only been described with sirolimus and temsirolimus. While extensive data have been published on sirolimus-induced lung toxicity, limited information about the pulmonary effects of temsirolimus exists in the literature.[1,6]

The association between sirolimus and pulmonary toxicity was first described in 2000 by Mahalati in two kidney transplant recipients.[24] Since then, 41 additional cases have been reported in the literature.[6] The series include 38 kidney transplants, 1 orthotopic liver transplant, 1 orthotopic heart transplant and 1 heart–lung transplant recipient. The onset of pneumonitis was variable ranging from within the first 6 months to 1 year after initiation of sirolimus. The most common presentation was dyspnea on exertion and dry cough followed by fatigue and fever. The radiological findings most frequently consist of bilateral patchy or diffuse alveolo-interstitial infiltrates. Pulmonary function tests demonstrated in some cases a restrictive pulmonary disease pattern or isolated reduction in the DLCO. Discontinuation or dose reduction of sirolimus resulted in clinical and radiological improvement in all cases within 3 weeks. The exact mechanism of sirolimus-induced toxicity has not clearly been established. Previously a dose-related effect and a cell-mediated autoimmune response were suggested.[9,24,25] More recently, Pham and colleagues proposed a T-cell mediated delayed type hypersensitivity mechanism based on the findings of striking alveolitis with alveolar lymphocytosis and a predominance of CD4-positive T-cells on flow cytometric analysis of bronchoalveolar lavage fluid in affected patients.[6,9] It was hypothesized that through its binding to plasma proteins sirolimus becomes immunogenic. An initial immune response would be evoked through the processing of sirolimus-protein complex by antigen presenting cells in the lungs such as alveolar type II lining cells, with subsequent T-cell recognition of the processed antigen complex, release of cytokines, and preferential differentiation of Th0 to Th1, and to a lesser extent, Th2 cells. Repeated exposure of sirolimus would result in antigen presentation, predominantly to Th1 cells, leading to Th1 activation, release of Th1 cytokines, recruitment and activation of macrophages and other inflammatory cells.

Temsirolimus-induced lung toxicity was first communicated by Atkins and colleagues after conducting a randomised phase II study in patients with advanced refractory renal cell carcinoma testing three different dose levels of the drug (25, 75 and 250 mg). Out of 111 patients, 6 (5%) were reported to have possible non-specific pneumonitis. Five of these patients were in the 75 mg cohort and 1 in the 25 mg cohort. Of these, 2 were withdrawn from additional treatment and 4 were re-

treated, with 2 patients experiencing recurrent pneumonitis.[20] Additional evidence of possible temsirolimus-associated lung toxicity has been recently reported in 3 phase II studies. Chan and colleagues conducted a randomised phase II trial of temsirolimus in patients with locally advanced or metastatic breast cancer. A hundred and nine patients were treated with weekly doses of either 75 or 250 mg of temsirolimus. One patient with advanced disease (1%) on the 75 mg cohort was hospitalised on day 7 and died on day 9 of a pneumonia that was considered as possibly related to the treatment.[26] More recently, Galanis and colleagues reported their data from another phase II trial in recurrent glioblastoma multiforme patients, where 65 patients were treated with weekly doses of 250 mg of temsirolimus. Two patients had grade 5 events possibly related to the treatment consisting of one severe pneumonitis and one pneumonia.[27] Pneumonitis has been described as well in a phase II trial of patients with relapsed or refractory mantle cell lymphoma.[28] Out of 35 patients treated with weekly doses of 250 mg of temsirolimus, 1 patient (3%) presented with a grade 3 pneumonitis possibly related to the treatment. No additional reports regarding temsirolimus-associated lung toxicity have been published on the literature.

In our series we observed a higher incidence of drug-induced pulmonary toxicity (8/22 or 36% of the patients) compared with the data published by Atkins and colleagues[20] and other series.[26–28] That fact could be due to the inclusion of routine CT thorax in the follow up of most of our patients, leading to the diagnosis of patients with little or no symptoms. In comparison with the experience with sirolimus, the percentage of asymptomatic patients is larger in our series. Whether this observation is drug-dependent or due to patient selection is unclear, while small sample sizes also preclude any meaningful comparisons between series. PFTs performed among selected patients in our series suggest that DLCO is one of the most sensitive parameter that becomes abnormal early on in DIP, implicating underlying lung abnormalities. Eighty percent of our patients who underwent PFTs showed a decrease in their DLCO. However the lack of pretreatment and serial PFTs in all patients may have led us to under-diagnose milder forms of pulmonary toxicity.

From the analysis of our series we described two radiological patterns associated with the pulmonary toxicity of temsirolimus: ground glass opacities with or without diffuse interstitial disease and lung parenchymal consolidation. The former has been described as the most common radiological finding in sirolimus-induced pulmonary toxicity while the latter pattern has not been associated with sirolimus. The exact mechanism of temsirolimus-induced pulmonary toxicity is unknown. Based on the data from Atkins and colleagues, this toxicity does not appear to be dose-dependent, as none of the 6 patients diagnosed with DIP were on the highest dose group of 250 mg/week in that study. Similarly, in our series, patients received low weekly doses of temsirolimus. In addition, other adverse effects that could be considered dose-dependent such as thrombocytopenia and hyperlipidemia, were not observed in any of our patients at the time of diagnosis of temsirolimus-associated pulmonary toxicity. A T-cell mediated delayed type hypersensitivity mechanism has been proposed to explain sirolimus toxicity, whether this theory is applicable to temsirolimus remains unclear.[25] The bronchoalveolar lavage obtained from 2 patients in our series was not sent for flow cytometry, thus limiting the information to support the T-cell mediated delayed type hypersensitivity mechanism. Pulmonary parenchymal changes induced by the immunological response may ensue with variable outcomes depending on pre-treatment conditions. We anecdotally observed that patients with a previous history of pulmonary disease presented with more severe architectural changes in the lung parenchyma after temsirolimus exposure. While it is possible that patients with underlying pulmonary conditions prior to temsirolimus treatment may have an increased risk of developing lung toxicity, this finding needs further validation. Due to the small number of patients in our series it is also difficult to conclude whether or not there is a causal link between this drug and the development of aspergillosis.

Regarding the management of this toxicity, in our experience, it should be based on clinical symptoms and results of PFTs. We propose that asymptomatic patients with only radiological changes would not require specific therapies or drug interruptions. Those with increasing clinical symptoms in conjunction with a decrease in DLCO on PFTs would benefit from drug discontinuation and probably high doses of steroids for a short period of time. Patients with underlying pulmonary pathologies prior to initiation of temsirolimus must be monitored with caution. Any clinical or radiological changes observed in this patient population while on temsirolimus should prompt drug discontinuation and further investigations performed to rule out infectious complications.

In summary, from our experience temsirolimus was associated with a higher rate of pulmonary toxicity than previously reported in the literature. The mechanism of action of this toxicity has not clearly been established and its clinical presentation may be variable. We proposed that the management of this phenomenon be based upon the clinical situation and pulmonary functions. Further prospective pulmonary investigations with a larger number of patients are needed to confirm this findings, as well as to provide better insight into the pathogenesis of this phenomenon and its proper management.

Conflicts of interest statement

The authors have no conflicts of interest to disclose.

REFERENCES

1. Vignot S, Faivre S, Aguirre D, Raymond E. mTOR-targeted therapy of cancer with rapamycin derivatives. *Ann Oncol* 2005;**16**(4):525–37.
2. Hidalgo M, Rowinsky EK. The rapamycin-sensitive signal transduction pathway as a target for cancer therapy. *Oncogene* 2000;**19**(56):6680–6.
3. Podsypanina K, Lee RT, Politis C, Hennessy I, Crane A, Puc J, et al. An inhibitor of mTOR reduces neoplasia and normalizes p70/S6 kinase activity in Pten$^{+/-}$ mice. *Proc Natl Acad Sci USA* 2001;**98**(18):10320–5.

4. Guba M, von Breitenbuch P, Steinbauer M, Koehl G, Flegel S, Hornung M, et al. Rapamycin inhibits primary and metastatic tumor growth by antiangiogenesis: involvement of vascular endothelial growth factor. *Nat Med* 2002;**8**(2):128–35.
5. Shi Y, Frankel A, Radvanyi LG, Penn LZ, Miller RG, Mills GB. Rapamycin enhances apoptosis and increases sensitivity to cisplatin in vitro. *Cancer Res* 1995;**55**(9):1982–8.
6. Pham PT, Pham PC, Danovitch GM, Ross DJ, Gritsch HA, Kendrick EA, et al. Sirolimus-associated pulmonary toxicity. *Transplantation* 2004;**77**(8):1215–20.
7. Morelon E, Stern M, Kreis H. Interstitial pneumonitis associated with sirolimus therapy in renal-transplant recipients. *N Engl J Med* 2000;**343**(3):225–6.
8. Singer SJ, Tiernan R, Sullivan EJ. Interstitial pneumonitis associated with sirolimus therapy in renal-transplant recipients. *N Engl J Med* 2000;**343**(24):1815–6.
9. Morelon E, Mamzer-Bruneel MF, Peraldi MN, Kreis H. Sirolimus: a new promising immunosuppressive drug. Towards a rationale for its use in renal transplantation. *Nephrol Dial Transplant* 2001;**16**(1):18–20.
10. Yu K, Toral-Barza L, Discafani C, Zhang WG, Skotnicki J, Frost P, et al. mTOR, a novel target in breast cancer: the effect of CCI-779, an mTOR inhibitor, in preclinical models of breast cancer. *Endocr Relat Cancer* 2001;**8**(3):249–58.
11. Ha L. The rapamycin derivative RADOO1 in oncology: What is the endpoint? In: *AACR-NCI-EORTC Internal Conference. Molecular Cancer and Cancer therapeutics*; 17–21 November 2003; Boston, MA; 2003. p. 259–60.
12. Mita MM, Goldston ML, et al. Phase I pharmacokinetic (PK) and pharmacodynamic (PD) study of AP 23573, an mTOR inhibitor administered IV daily × 5 every other week in patients with refractory or advanced malignancies. In: *Proc Am Soc Clin Oncol*; 2004; New Orleans: Meeting proceedings American Society of Clinical Oncology; 2004.
13. Chan S. Targeting the mammalian target of rapamycin (mTOR): a new approach to treating cancer. *Br J Cancer* 2004;**91**(8):1420–4.
14. Grunwald V, DeGraffenried L, Russel D, Friedrichs WE, Ray RB, Hidalgo M. Inhibitors of mTOR reverse doxorubicin resistance conferred by PTEN status in prostate cancer cells. *Cancer Res* 2002;**62**(21):6141–5.
15. Dudkin L, Dilling MB, Cheshire PJ, Harwood FC, Hollingshead SG, Arbuck SG, et al. Biochemical correlates of mTOR inhibition by the rapamycin ester CCI-779 and tumor growth inhibition. *Clin Cancer Res* 2001;**7**(6):1758–64.
16. Shi Y, Gera J, Hu L, Hsu JH, Bookstein R, Li W, et al. Enhanced sensitivity of multiple myeloma cells containing PTEN mutations to CCI-779. *Cancer Res* 2002;**62**(17):5027–34.
17. Geoerger B, Kerr K, Tang CB, Fung KM, Powell B, Sutton LN, et al. Antitumor activity of the rapamycin analog CCI-779 in human primitive neuroectodermal tumor/medulloblastoma models as single agent and in combination chemotherapy. *Cancer Res* 2001;**61**(4):1527–32.
18. Raymond E, Alexandre J, Faivre S, Vera K, Materman E, Boni J, et al. Safety and pharmacokinetics of escalated doses of weekly intravenous infusion of CCI-779, a novel mTOR inhibitor, in patients with cancer. *J Clin Oncol* 2004;**22**(12):2336–47.
19. Baselga JFP, Gil M, et al. Phase 2-3 study of CCI-779 in combination with letrozole in postmenopausal women with locally advanced or metastatic breast cancer: preliminary results. *Proc Am Soc Clin Oncol* 2004;**23**:13. Abstract 544.
20. Atkins MB, Hidalgo M, Stadler WM, Logan TF, Dutcher JP, Hudes GR, et al. Randomized phase II study of multiple dose levels of CCI-779, a novel mammalian target of rapamycin kinase inhibitor, in patients with advanced refractory renal cell carcinoma. *J Clin Oncol* 2004;**22**(5):909–18.
21. Tabernero JR, Burris H, Casado E, Macarulla T, Jones S, Dimitrijevic S, et al. A phase I study with tumor molecular pharmacodynamic (MPD) evaluation of dose and schedule of the oral mTOR-inhibitor Everolimus (RAD001) in patients (pts) with advanced solid tumors. *Proc Am Soc Clin Oncol* 2005;**23**(16s):193s. Abstract 3007.
22. Chawla SP, Chua V, Menendez LR, Eilber FC, Eckardt JJ, Daly ST, et al. A phase II study of AP23573 (an mTOR inhibitor) in patients (pts) with advanced sarcomas. *Proc Am Soc Clin Oncol* 2005;**23**(16s):833s. Abstract 9068.
23. Feldman E, Roboz G, Yee K, Curcio T, Rivera VM, Albitar M, et al. A phase 2 clinical trial of AP23573, an mTOR inhibitor, in patients with relapsed or refractory hematologic malignancies. *Proc Am Soc Clin Oncol* 2005;**23**(16s):592s. Abstract 6631.
24. Mahalati K. Bronchiolitis obliterans and organizing pneumonia in renal transplant recipients. *Transplantation* 2000;**69**:1581.
25. Morelon E, Stern M, Israel-Biet D, Correas JM, Danel C, Mamzer-Bruneel MF, et al. Characteristics of sirolimus-associated interstitial pneumonitis in renal transplant patients. *Transplantation* 2001;**72**(5):787–90.
26. Chan S, Scheulen ME, Johnston S, Mross K, Cardoso F, Dittrich C, et al. Phase II study of temsirolimus (CCI-779), a novel inhibitor of mTOR, in heavily pretreated patients with locally advanced or metastatic breast cancer. *J Clin Oncol* 2005;**23**(23):5314–22.
27. Galanis E, Buckner JC, Maurer MJ, Kreisberg JI, Ballman K, Boni J, et al. Phase II trial of temsirolimus (CCI-779) in recurrent glioblastoma multiforme: a North Central Cancer Treatment Group Study. *J Clin Oncol* 2005;**23**(23):5294–304.
28. Witzig TE, Geyer SM, Ghobrial I, Inwards DJ, Fonseca R, Kurtin P, et al. Phase II trial of single-agent Temsirolimus (CCI-779) for relapsed mantle cell lymphoma. *J Clin Oncol* 2005;**23**(23):5347–56.