Evolving Strategies in the Treatment of Tuberous Sclerosis Complex-associated Angiomyolipomas (TSC-AML)

Anil Kapoor, Louis Girard, Jean-Baptiste Lattouf, York Pei, Ricardo Rendon, Paul Card, and Alan So

Tuberous sclerosis complex (TSC) is a rare autosomal dominant genetic disorder characterized by the development of numerous benign tumors that occur in multiple organ systems throughout the lifetime of the affected individuals. Renal angiomyolipomas occur in up to 80% of TSC patients, and chronic kidney disease from increasing tumor burden is the primary cause of TSC-related mortality. Our review evaluates evidence for localized and systemic therapy in the management of TSC-angiomyolipomas. Urologists or nephrologists experienced in TSC disease should coordinate the care of TSC patients with renal involvement to improve care and reduce costs. UROLOGY 89: 19–26, 2016. © 2016 Elsevier Inc.

Tuberous sclerosis complex (TSC) is an autosomal dominant genetic disorder that affects up to 1 million people worldwide.[1] The overall estimated incidence of TSC disease is 1 case per 6000 births,[1] suggesting that up to 6000 Canadians could be living with this disease. TSC is a potentially debilitating and progressive condition characterized by the development of numerous benign tumors (eg, hamartomas) affecting a variety of organs throughout the patient's lifetime. These tumors may affect multiple organs ubiquitously, including the brain, kidneys, skin, heart, and lungs, resulting in highly diverse clinical manifestations of varying severity and substantial morbidity and mortality depending on the type and number of organs involved.

Although TSC is often inherited, approximately two-thirds of known cases are the result of sporadic mutations.[2] Products of the *TSC1* and *TSC2* genes are integral to the normal function of the mechanistic target of rapamycin (mTOR) signaling pathway and lie at the heart of TSC pathogenesis.[1] Mutations in *TSC1* and/or *TSC2* prevent formation of the active TSC1/TSC2 heterodimer, which normally inhibits mTOR activity, leading to hyperactive mTOR signaling and dysregulated cellular processes.[1,3] Mutations in *TSC2* are more common (70%-80%) than *TSC1* mutations[1] and are associated with more clinical manifestations as well as greater disease severity, including a higher degree of renal involvement.[1,4] Deletions involving both the *TSC2* and polycystic kidney disease (*PKD1*) type 1 genes can result in *TSC2/PKD1* contiguous gene syndrome[5] which can result in early and severe renal failure.

A TSC diagnosis involves a clinical exam, imaging, and blood work to assess the extent of disease and organ involvement. Updated criteria from the 2012 International Tuberous Sclerosis Complex Consensus Conference specify 11 major and 9 minor disease features used to establish a clinical TSC diagnosis.[6] Major features include the presence of hypomelanotic macules (≥3, at least 5-mm diameter), angiofibromas (≥3) or fibrous cephalic plaque, ungual fibromas (≥2), Shagreen patch, multiple retinal hamartomas, cortical dysplasias, subependymal nodules, subependymal giant cell astrocytoma (SEGA), cardiac rhabdomyoma, lymphangioleiomyomatosis (LAM), and angiomyolipomas (≥2). Minor features include "confetti" skin lesions, dental enamel pits (>3), intraoral fibromas (≥2), retinal achromic

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patch, multiple renal cysts, and nonrenal hamartomas. Current guidelines consider the presence of two major features, or one major feature plus ≥2 minor features sufficient for a definite TSC diagnosis. One major feature or ≥2 minor features indicate a possible diagnosis of TSC.[6] Genetic testing can establish and/or confirm a diagnosis and guide genetic counseling.[6,7] Although a confirmed pathogenic *TSC1* or *TSC2* mutation is sufficient as an independent criterion for a TSC diagnosis,[6,8] mutations fail to be detected in 10%-25% of patients with clinically confirmed TSC.[6] The determination of the type of gene mutation, either TSC1 or TSC2, does not generally impact the overall management of TSC-AML.

Renal angiomyolipomas (AMLs) occur in up to 80% of TSC patients.[4,9] TSC-associated AMLs (TSC-AMLs) are (1) mostly benign, slow-growing kidney tumors that typically require monitoring and possible intervention in adults due to their progressive nature, and (2) frequently bilateral and can result in substantial clinical burden.[1,10] Lesions ≥4 cm in diameter are at increased risk for spontaneous bleeding due to vessel rupture,[11] and AML vascular aneurysms ≥5 mm in diameter are strongly predictive of acute renal hemorrhage both in TSC and non-TSC associated AMLs.[9,11] TSC-AML parenchymal invasion can damage functional renal tissue,[9] and there is a prevalence of renin-dependent hypertension among TSC patients.[12] Chronic renal failure often requiring dialysis occurs in approximately 15% of TSC patients due to loss of renal parenchyma from progressive disease or local resection/embolization of the TSC-AML[1,13,14] representing a leading cause of TSC-related death in adult patients.[9,15]

Continued surveillance of AMLs is imperative from the point of diagnosis onward to monitor progression, detect new tumor emergence, screen for malignancies, and manage secondary complications. Recommended surveillance for TSC patients with renal manifestations consists of abdominal screening with magnetic resonance imaging (MRI) or ultrasound in younger patients every 2-5 years depending on tumor burden,[16,17] MRI or computed tomography in older patients (>20 years) every 1-3 years,[7,16,18,19] and more active monitoring for patients with larger and/or growing lesions.[16,17,20] When possible, MRI is the preferred imaging modality[7] due to its ability to resolve fat-poor AML lesions,[21] which account for up to 39% of TSC-AMLs,[16] as well as reduced radiation exposure compared with computed tomography imaging. Surveillance should also include assessment of renal function through determination of glomerular filtration rates as well as random quantification of proteinuria and blood pressure at least annually.[7] Secondary complications such as hypertension should be managed appropriately.

Patients with progressive TSC-AML often develop multiple, larger lesions over time, leading to symptomatic disease and secondary complications. TSC-related symptoms include acute retroperitoneal hemorrhage, hematuria, palpable mass, flank pain, urinary tract infections, renal failure, or hypertension. Although surgical interventions are often used to manage acute renal hemorrhage,[7] until recently there have been no treatments available to arrest underlying disease processes. There is mounting evidence exploring the role of selective arterial embolization and ablative techniques in disease management,[7,22-30] and insights on hyperactive mTOR signaling have also led to the clinical development of mTOR inhibitors for treating TSC-related tumor growth (Fig. 1).[10,31-36]

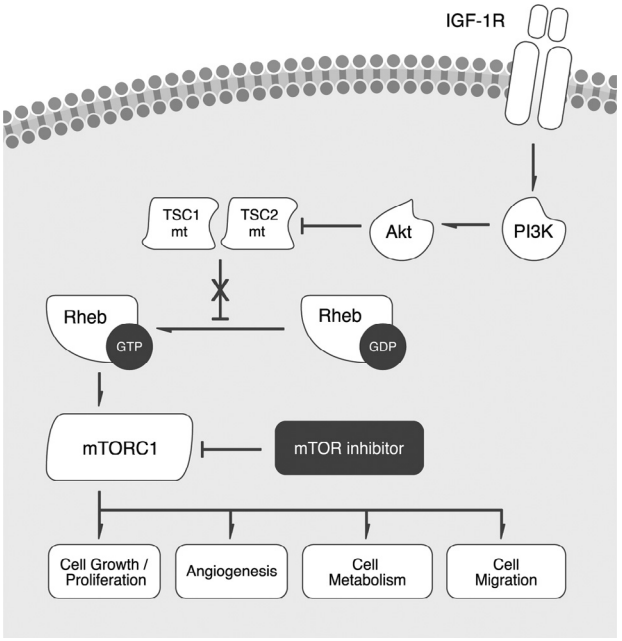

Figure 1. mTOR inhibitors restore inhibition of mTOR signaling in patients with mutations in TSC1 or TSC2. TSC1 and TSC2 form a heterodimeric protein complex (hamartin-tuberin) involved in the regulation of many cellular processes. The TSC1-TSC2 heterodimer activates a GTP-ase, preventing phosphorylation of the Ras homolog enriched in brain (Rheb) GAP protein and subsequently inhibiting activation of the mTOR comlex 1 (mTORC1). Mutation in TSC1 and/or TSC2 results in loss of function, preventing the formation of active complex which leads to hyperactive mTOR signaling and dysregulated cell activities. Inhibitors of mTOR signaling are being investigated for therapeutic benefit in TSC-AML. Akt, protein kinase B; GDP, guanosine diphosphate; GTP, guanosine triphosphate; mTORC1, mammalian target of rapamycin complex 1; PI3K, phosphoinositide 3-kinase; Rheb, Ras homolog enriched in brain protein; TSC1, tuberous sclerosis 1 protein; TSC2, tuberous sclerosis 2 protein.

The purpose of this review is to update clinical trial data and provide practical and clear guidance on use of localized and systemic interventions in the treatment of TSC-AML.

METHODS

A literature review was conducted (all time to February 5, 2015) to identify trials addressing the treatment of TSC-AML disease using the MEDLINE database (PubMed—all time) and the European Association of Urology Congress and Annual Meeting of the American Urological Association conference databases up to 2014. Search queries

and results were restricted to the English language, and search terms included "tuberous sclerosis" and "angiomyolipoma" and respective aliases. Literature search results were reviewed to identify localized and systemic interventions for the treatment of TSC-AML disease with a focus on best available evidence.

FINDINGS

Localized Therapy

A total of 106 records addressing the use of localized therapy in the treatment of TSC-AML were identified. No clinical trials were identified, with the best available evidence consisting of 97 case reports/series and 9 retrospective analyses. The majority of studies explored the role of surgery in treating symptomatic disease, with a general trend away from radical surgical interventions such as total nephrectomy and toward minimally invasive procedures.[7,37]

A considerable number of reports have studied the role of minimally invasive procedures including selective arterial embolization or conservative ablative therapy for TSC-AML management in asymptomatic patients,[22-24,26,27] with a trend toward their use for larger tumors (>3.5-4 cm in diameter). Retrospective studies have reported tumor reduction, hemorrhage prevention, preservation of kidney function,[24,26] and low rates of procedure-related mortality and serious complications.[25] However, embolization is not without risk. A retrospective institutional review indicated that embolization is associated with inflammatory responses causing significant fever and pain in nearly 90% of patients, which may be reduced to approximately 30% with the use of a short course of tapering dose of prophylactic steroids (250 mg/m^2 of methylprednisolone).[20,38] Moreover, a large Dutch observational study (n = 244) with long-term follow-up (median of 15.8 years), reported significantly increased risk of secondary complications such as hypertension (HR [hazard ratio] = 3.04, $P < .001$) and anemia (HR = 3.92, $P < .001$), with no significant reductions in mortality rates (all-case: HR = 0.49, $P = .4$; renal-related: HR = 0.53, $P = .4$) for patients undergoing elective embolization compared with no surgical intervention.[22] This study also indicated that patients with large growing asymptomatic AMLs will likely require embolization every 7 to 11 years, which could contribute to accelerated kidney function decline.[22]

Systemic Therapy

A total of 20 records reporting use of pharmacologic interventions in the treatment of TSC-AML were found, including three phase I/II trials evaluating sirolimus[33-35] and one prospective and one retrospective phase III evaluation of everolimus.[10,32,39] Sirolimus, administered at a variable dosing schedule dependent on plasma levels and response, was the first mTOR inhibitor to demonstrate activity in one phase I/II study[33] and two phase II trials[34,35] for the treatment of TSC-AML. Sirolimus studies evaluated patients with a diagnosis of TSC,[34] TSC or SL,[33] and TSC or sporadic LAM,[35] with at least one AML ranging from ≥1 to ≥ 2cm in diameter. Doses at study initiation were 0.25 mg/m^2 or 1 mg/d or 6 mg on day 1 then 2 mg daily,[35] with doses adjusted to achieve blood levels from 1 to 15 ng/mL.[33-35] These studies resulted in TSC-AML response rates of 44.4% to 58.8%,[34,35] prompting further investigation of mTOR inhibitors for TSC-AML.

The EXIST-1 (examining everolimus in a study of TSC) phase III trial evaluated the activity and safety of everolimus vs placebo in patients with TSC SEGA tumors.[31] Forty-four of the 117 SEGA patients enrolled in the trial had at least one baseline renal AML lesion ≥1 cm in longest diameter, and 30 of these patients receiving everolimus 4.5 mg/m^2 daily (titrated to blood trough levels of 5–15 ng/mL) were compared to 14 patients receiving placebo. Patients receiving everolimus had an improved rate of AML response (53.3% vs 0%, defined as reduction in the sum of volumes of all target lesions ≥50% relative to baseline). Adverse events (AEs) were higher in patients treated with everolimus compared to placebo, which included mouth ulceration (43% vs 14%), convulsions (30% vs 29%) and stomatitis (27% vs 7%).

The randomized EXIST-2 phase III trial was initiated to prospectively evaluate everolimus (10 mg daily) compared to placebo in 118 patients with larger AML lesions (≥3 cm in longest diameter) and a definitive diagnosis of TSC or LAM.[10] Baseline characteristics between arms were well balanced and representative of normal TSC epidemiology, although a greater proportion of patients on the everolimus arm had TSC-SEGA tumors compared with the placebo group (54% vs 36%).[1,10] Everolimus resulted in superior AML responses (reduction in the sum of all target AML volumes ≥50% relative to baseline and absence of AML progression) compared to placebo (42% vs 0%, $P < .0001$), and no patients receiving placebo showed a response at any time point (Table 1). None of the patients who achieved a response had progressed at the data cutoff date, with all AML responses ongoing for 10 to 85 weeks at data cutoff. Everolimus was significantly superior to placebo in median time to AML progression (NYR vs 11.4 months; HR 0.08, 95% confidence interval 0.02-0.37, $P < .0001$).

AEs in EXIST-2 were primarily grade 1 or 2 (Table 1). The most common AEs of any grade reported in ≥20% of patients on the everolimus arm were infection (65%), stomatitis (48%), nasopharyngitis (24%), acne-like skin lesions (22%), headache (22%), hypercholesterolemia (20%), and cough (20%). Grade 3 or 4 AEs were uncommon in this study. One death from convulsion (due to status epilepticus) occurred, but was not considered drug related.[10] Overall, everolimus was well tolerated, reflected by the lower rate of discontinuation due to AEs for everolimus (4%) compared with placebo (10%).[10]

Following positive results from the original data cutoff, all patients were offered open-label everolimus in the study extension phase of the EXIST-2 trial. Response rates improved from 42% in the initial report (median duration of treatment exposure [mDOE] of 8.7 months) to 56.3% at an mDOE of 39.8 months (Table 2). There was a trend toward increased rates of more common any-grade AEs over

Table 1. Phase III efficacy and select safety outcomes of everolimus in asymptomatic patients with TSC-AML (Bissler et al[10] EXIST-2 NCT00790400, Phase III)

	Everolimus 10 mg Daily		Placebo	
Population, n	79		39	
Median age (years)	32		29	
[range]	[18-61]		[18-58]	
Response rate (%), [95% CI]	42*, [31-53] $P < .0001$		0, [0-9]	
Discontinuation due to adverse events n (%)	3 (4)		4 (10)	
Dose reductions or interruptions due to adverse events, n (%)	38 (48)		8 (21)	
Adverse events†, n (%)	All Grades	Grade 3/4	All Grades	Grade 3/4
Infections (general)	51 (65)	–	28 (72)	–
Stomatitis	38 (48)	1 (1)	3 (8)	0
Nasopharyngitis	19 (24)	0	12 (31)	0
Headache	17 (22)	0	7 (18)	1 (3)
Acne-like skin lesions	17 (22)	0	2 (5)	0
Cough	16 (20)	0	5 (13)	0
Hypercholesterolemia	16 (20)	0	1 (3)	0
Aphthous stomatitis	15 (19)	2 (3)	4 (10)	0
Fatigue	14 (18)	1 (1)	7 (18)	0
Nausea	13 (16)	0	5 (13)	0
Mouth ulceration	13 (16)	2 (3)	2 (5)	0
Vomiting	12 (15)	0	2 (5)	0
Urinary tract infection	12 (15)	0	6 (15)	0

AML, angiomyolipoma; CI, confidence interval; EXIST, examining everolimus in a study of TSC; TSC, tuberous sclerosis complex.
* Reduction in AML volume (sum of volumes of all target AMLs identified at baseline) of 50% or more relative to baseline and absence of AML progression, defined as one or more of: increase from the nadir of 25% or more in AML volume (sum of volumes of all target AMLs identified at baseline) to greater than baseline; appearance of a new AML at least 1 cm in longest diameter; increase from nadir of 20% or more volume of either kidney to greater than baseline; or grade 2 AML-related bleeding.
† In ≥ 15% of patients.

Table 2. Long-term efficacy and safety outcomes of EXIST-2 extension trial

EXIST-2 extension trial	Primary [10]	Expansion I [40]	Expansion II [39]
Median duration of exposure (months)	8.7*	29.0	39.8
Data cutoff date	June 2011	May 2013	April 2014
Response rate (%)	42	54	56.3
[95% CI]	[31-53]	[44-63]	[46.6-65.6]
Any grade adverse events in ≥ 20% patients (%)†			
Stomatitis (%)	48	43	42.9
Nasopharyngitis (%)	24	43	44.6
Acne (%)	22	30	31.3
Headache (%)	22	30	31.3
Cough (%)	20	21	21.4
Hypercholesterolemia (%)	20	30	35.7

Abbreviations as in Table 1.
* Based on 4.35 week per month conversion factor.
† Based on adverse event frequencies in primary report.

time, with the exception of stomatitis which decreased slightly over the same period (48% to 42.9%).[39]

DISCUSSION

TSC-AML is a progressive disorder that may result in significant morbidity and even mortality. Due to substantial variability in the number, size, growth kinetics, and location of TSC-AMLs, an individual approach to treatment which is evidence-based and optimizes the preservation of functional kidney tissue is integral for optimizing both outcomes and quality of life.[7,41,42]

What Treatment Is Warranted for Symptomatic Disease?

Advanced TSC-AMLs may lead to numerous symptoms. Less severe symptoms (flank pain, hypertension, or minor bleeding) may be managed with appropriate rest and supportive care, and more severe symptoms such as acute hemorrhage have been treated using localized therapy, with a trend toward the use of minimally invasive procedures, depending on the extent and nature of the disease.[7,37] Localized therapy for TSC-AML is well established and often lifesaving, although with limited clinical trial data evaluating long-term kidney function following these procedures,

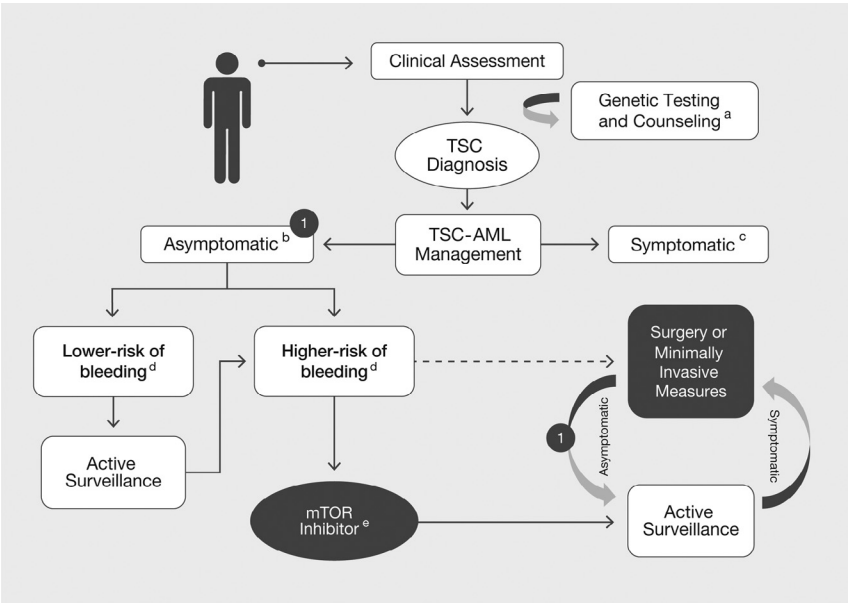

Figure 2. Management of TSC-AML. Dark boxes denote treatment options; dashed line denotes a lack of level 1 evidence. AML, angiomyolipoma; mTOR, mechanistic target of rapamycin; TSC, tuberous sclerosis complex. [a] Genetic testing and counseling helpful in establishing or confirming a diagnosis, to inform family planning or assessing familial risk. [b] mTOR-inhibitor naïve patients. [c] Symptoms may include acute retroperitoneal hemorrhage, hematuria, palpable mass, flank pain, urinary tract infections, renal failure, or hypertension. [d] Additional elements that may determine risk for secondary complications include tumor size ≥ 4 cm, the presence of aneurysms ≥5 mm, growth patterns, bilateral lesions, tumors located in critical or unresectable areas, increased disease burden, or low functional kidney tissue reserves. [e] Everolimus is the only agent with Level 1 evidence and that is currently approved for this indication.

treatment of acute hemorrhage should be minimally invasive whenever possible (Fig. 2). Conservative selective embolization with or without the use of corticosteroids (250 mg/m^2 of methylprednisolone) is an established approach.[7,38] There remains a pressing need for ongoing research into the risks and benefits of various minimally invasive procedures for symptomatic TSC-AMLs.

When Are Interventions Warranted for Asymptomatic Patients?

Some AML patients with a low clinical burden may experience prolonged periods of asymptomatic disease (low-risk). Other patients may be at a higher risk of secondary complications (high-risk), including those with lesions ≥4 cm or aneurysms ≥5 mm in diameter, which have a greater risk of hemorrhage,[9,11] as well as patients with a greater overall disease burden, bilateral lesions, low functional kidney reserves, rapidly growing tumors or critically located lesions. Active surveillance is the preferred approach for low-risk patients with asymptomatic disease, and the potential risks and benefits of other interventions, either conservative localized or pharmacological, should be carefully considered in asymptomatic high-risk patients (Fig. 2). High-risk patients with long-term stable disease may also be managed preferentially with conservative measures.

When Are Pharmacological Interventions Warranted in Asymptomatic Disease?

Sirolimus was the first agent to demonstrate activity within a clinical trial context, although phase III data are lacking and further study is required to establish optimal dosing protocols for sirolimus in TSC-AML disease.

Everolimus is the only agent for which phase III clinical trial data are available.[10,31] Everolimus demonstrated safety and activity in a retrospective sub-group of SEGA patients with AML disease from the EXIST-1 trial, although these findings remain hypothesis generating because this analysis was retrospective and patients were not randomized based on the presence, size, or growth of AML lesions.[32] The phase III EXIST-2 trial of everolimus randomized patients with larger lesions (≥3 cm in diameter),[10,39] and findings from this study are more compelling as the study was prospectively designed for TSC-AML. The everolimus arm showed significantly improved response rates (42% vs. 0%) and median time to AML progression (median: NYR vs 11.4 months) compared with placebo ($P < .001$ for both).[10] However, this study failed to directly assess the incidence of renal hemorrhage, long-term kidney function, or the need for additional interventions, precluding a direct link between outcomes and overall quality of life. Nevertheless, given the established correlation between larger tumor size and hemorrhage risk,[11] it is plausible that prolonged reduction of AML tumor size from the use of mTOR inhibitors could

reduce secondary complications and preserve functional kidney tissue, particularly in high-risk patients. The majority of AEs were grades 1 and 2 in nature, and grade 3/4 AEs were uncommon.[10] The low rates of discontinuation due to AEs for everolimus in EXIST-2 (4% vs 10% for placebo), as well the low rate of treatment-related grade 3/4 AEs in the EXIST-1 subgroup analysis (6.7% vs 20% overall),[32] suggest that AEs were manageable and not always related to the study drug.

Everolimus should only be considered in high-risk asymptomatic patients (growing lesions ≥4 cm) with increased risk of secondary complications (Fig. 2), or patients who have recovered from a symptomatic event (AML bleed or pain) and have stabilized. Surveillance for tumor growth, blood pressure, and renal function should continue during treatment, initially every 6 to 8 weeks until stabilization, then every 3 to 4 months thereafter. Patients should be educated on AEs, particularly those which are potentially severe such as pneumonitis or with early onset such as stomatitis or anemia.[43] Treatment should be discontinued followed by active monitoring if patients present with signs of acute or chronic kidney failure, rapidly increasing proteinuria, or in anticipation of surgery (stop 1 week prior to surgery and reinitiate 1 week after surgery, assuming there are no wound complications). Although select patients in the EXIST-2 trial remained on treatment for up to 3 years, the optimal duration of everolimus therapy remains unclear. Further research is needed to prospectively evaluate long-term quality of life outcomes and optimal treatment strategies in patients receiving mTOR inhibitors for TSC-AML.

When Is Surgical Intervention Warranted for Asymptomatic Disease?

Although localized therapy is primarily used to treat acute complications such as hemorrhage, minimally invasive procedures and surgery are increasingly being studied to prevent complications in asymptomatic TSC-AML patients.[22,27,37] Loco-regional techniques such as radiofrequency ablation, cryoablation, and microwave ablation have also been explored for small sporadic AML lesions, and may play a role in treating TSC-specific disease.[27-30] However, evidence supporting the use of these modalities for disease management is limited to case reports and retrospective reviews,[22-24,26,27] with no randomized clinical trial data. Additionally, studies generally neglected to evaluate long-term outcomes, and some reports suggest the potential for an increased rate of secondary complications, the possibility of reduced long-term kidney function, and the need for continued interventions that may further compromise renal function.[22] The benefit of localized therapy for asymptomatic disease therefore remains speculative and their impact on quality of life uncertain. We therefore recommend that consideration of conservative measures be limited to high-risk patients after failure of an mTOR inhibitor.[7] Additional phase III research is required to establish the short and long-term risks and benefits of surgical interventions for TSC-AML disease management.

When Should TSC-AML Lesions be Biopsied?

Patients with TSC disease may be predisposed toward malignancies and TSC-related lesions, although usually benign, can be fat-poor (up to 39%), making them difficult to differentiate from malignant tumors.[16,20] TSC-associated renal cell carcinomas are relatively uncommon (2%-5%),[44,45] and have unique clinicopathologic features including younger age at diagnosis (often in children or young adults),[45] female predominance, multiplicity, AML association, a more indolent clinical course, and distinct morphologies.[46,47] In general, biopsy is recommended when fat-poor lesions appear individually, show rapid growth, calcifications, tissue necrosis, an anechoic rim, intratumoral cysts, any ambiguity regarding diagnosis, or exhibit other suspicious characteristics.[7,16,20,48]

Is There a Need for Coordinated TSC-AML Care?

Ongoing care of TSC disease requires involvement from a variety of specialists. This network usually involves urologists, nephrologists, family practitioners, geneticists, genetic counselors, neurologists, psychiatrists, dermatologists, respirologists/pulmonologists, ophthalmologists, interventional radiologists, and dentists or oral surgeons. Given the progressive nature of TSC, multidisciplinary care coordinated through dedicated clinics or virtual networks may improve outcomes and reduce costs.[7,49,50] TSC-AML management by a team of specialists coordinated by a urologist or nephrologist experienced in TSC disease is therefore recommended.

SUMMARY AND CONCLUSION

TSC is a progressive disorder that can be associated with substantial morbidity and mortality. Renal angiomyolipomas are a common adult clinical manifestation of TSC that requires careful surveillance and management to prevent potentially life-threatening complications. Active surveillance is the preferred approach for low-risk patients with asymptomatic disease. Conservative selective embolization is recommended for patients experiencing renal hemorrhage, and conservative ablative therapies may have a future role for treating smaller lesions. Everolimus should be considered in high-risk asymptomatic patients, or those patients recovered from a symptomatic event. Ongoing research into the long-term effects of both localized and systemic therapy is required, and urologists or nephrologists experienced in TSC disease should coordinate specialist care to improve long-term outcomes for TSC patients with renal involvement.

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