Michele R. Sassi. *Gondolas, Venice, Italy.* Photograph.

To use targeted therapies optimally for treatment of metastatic kidney cancer, clinical issues besides those addressed in pivotal treatment trials should be recognized.

Targeted Therapy of Kidney Cancer: Keeping the Art Around the Algorithms

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Background: *Therapy for metastatic kidney cancer is actively evolving, particularly in the results of registration drug trials that have led to the approval of vascular endothelial growth factor pathway drugs such as sorafenib, sunitinib, pazopanib, bevacizumab, and axitinib, with focus on patients with good- or intermediate-risk criteria and clear cell histology. Mammalian target of rapamycin (mTOR) drugs such as everolimus and temsirolimus pivotal trials emphasize experiences in the setting of prior treatment or high-risk features. Interferon and interleukin 2 also are part of the treatment algorithms.*

Methods: *The results of pivotal trials and the underlying context for the development of a cogent, cohesive treatment plan for an individual are reviewed, touching on decision points such as nephrectomy, metastasectomy, and medical initiation and discontinuation time points.*

Results: *To the extent that these drug therapies are essential for achieving best outcomes for patients, these pivotal trial results and associated guidelines exist within a multidimensional, multidisciplinary context of many other disease features, comorbid features, and non-drug treatment decisions. Other dimensions include investigational targeted therapies, patient selection strategies, surgical strategies, and immunotherapies, some of which are in active development.*

Conclusions: *Clinicians should work toward the best use of drug sequencing and selection strategies based on core data derived from prospective randomized trials. To address individual patient needs, they should also recognize and emphasize individualized goals, to the extent that these are different from issues that were directly addressed in the trials.*

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Dr Fishman participated in patient treatment or received payment for consultation relating to research trials for kidney cancer therapy sponsored by AVEO Pharmaceuticals Inc, Amgen Inc, Bayer AG, Bristol-Myers Squibb Company, GlaxoSmithKline Corp, Eastern Cooperative Oncology Group, Eisai Inc, Novartis Corp, Pfizer Inc, Prometheus, and SWOG. He participated in paid speaker bureaus or advisory boards relating to kidney cancer for Bayer AG, GlaxoSmithKline, Eisai, Novartis, Prometheus, and Seattle Genetics Inc, and served on the National Comprehensive Cancer Network kidney/testis committee.

Introduction

Planning the treatment approach for a patient differs from planning a trial. Approved drugs by the US Food and Drug Administration (FDA) for the treatment of advanced kidney cancer can be organized into the immunotherapy, vascular endothelial growth factor (VEGF)–axis drugs, and mammalian target of rapamycin (mTOR) groups. These drug therapies exist among major medical treatment choices such as nephrectomy, metastasectomy, radiation therapy, bone-directed treatment, and other supportive care, as well as investigational drugs within these and other categories, particularly tyrosine kinase inhibition beyond

VEGF. Clinicians and patients must make decisions about when to start, stop, or change treatment, and they need not exactly mimic decisions made in clinical trials. As is similar for many malignancies, anatomical, biological, or comorbid homogeneity characterizations are ill-suited for describing many patients with metastatic kidney cancer. However, for the purpose of trial design and comparison, dividing patients into high-, intermediate-, or low-risk groups is useful[1,2] because significant variations of important features exist among individuals (eg, anatomical pattern of spread, comorbidity, stated treatment goals and travel limitations, evident rate of growth, histological subtypes).

Although pivotal trials designed around product registration may dominate the early impressions of a new drug, as well as the FDA label,[3-12] they are a rudimentary guide for the decision processes outside the dichotomous questions directly addressed in these trials. Table 1[3-14] lists the drugs approved by the FDA for kidney cancer and the respective primary end points of the pivotal trial underlying the indication. Table 2[15-34] lists selected prospective randomized trials and their respective primary end points. Secondary end points, such as the incidence of adverse events, stratification by risk group, and overall survival (OS) in the context of crossover of most of the control group population at the point of progression, are of intense clinical interest; however, from a statistical perspective, they are not directly addressed by these trial experiences.

As more drugs are developed with differences of schedule, pharmacokinetics, and on- and off-target effects, we should be optimistic that there will be evolution of the empirical basis for tailoring drug choice and treatment sequencing, with fewer assumptions about features of the population disease. Although many trials to address differences of population features will never be performed, assumptions about the timing of treatment as determinant of the biological features of the cancers (eg, "up front," "after progression through a VEGF drug") are made when organizing clinical trials. The assumptions are not intended to be misrepresentative, but the guidelines derived from these trials are made from the vantage point of those assumptions. Guidelines derived from

Table 1. — Selected Pivotal Trial Results Used for Consensus Recommendations of Drug Selection

Study Drug	Main Inclusion Features	Primary End Point	Comments and Secondary End Points
VEGF Group[a]			
Sunitinib[3]	First-line	PFS of sunitinib superior to interferon	OS difference observed but diluted because of crossover
Sorafenib[4]	Second-line, mostly after interferon	OS of sorafenib not statistically better	PFS of sorafenib superior to placebo; crossover at disease progression
Bevacizumab[5]	SWOG: first-line, most had prior nephrectomy	PFS of bevacizumab + interferon superior to single-agent interferon	No significant OS difference
Bevacizumab[6]	EORTC: first-line, required prior nephrectomy	PFS of bevacizumab + interferon superior to single-agent interferon	No significant OS difference
Pazopanib[7,8]	First-line or postimmunotherapy second-line	PFS of pazopanib superior to placebo	No significant OS difference High crossover
Axitinib[9,10]	Exactly second-line, most after prior VEGF drug, mostly sunitinib	PFS of axitinib superior to sorafenib	No significant OS difference; did not use sorafenib → axitinib crossover
mTOR Group			
Temsirolimus[11]	High-risk features Only trial concentrating those patients Allowed non–clear cell patients (~ 19%)	OS better than interferon group	PFS not significantly different
Everolimus[12]	≥ 1 prior anti-VEGF therapy	PFS of everolimus better than placebo	No significant OS difference Very high crossover
Immunotherapy[b]			
Interleukin 2, aldesleukin	No randomized registration trials	- 20 years of experience of some durable complete responses - Randomized trials vs low-dose regimens[13,14] show consistent complete responses with high durability but at frequency too low to affect median OS	

[a] All of these VEGF studies were limited to clear cell type kidney cancer.

[b] Practically speaking, used mostly in clear cell kidney cancer.

mTOR = mammalian target of rapamycin, OS = overall survival, PFS = progression-free survival, VEGF = vascular endothelial growth factor.

trials about selecting drugs are general, and they encompass guidelines for treatments for subsets of the population subtly or overtly divergent from the studied groups as well as those with differing disease biology, timelines, medical needs, or treatment goals. Fig 1 illustrates several concepts for practical patient treatment that largely exist outside of clinical trials, as well as the corresponding guidelines summarizing those experiences. Some reviews focused on summarizing the primary end point data of those prospective randomized trials and continue to be of interest.[35-37]

Guidelines address practical aspects of high level-of-evidence consensus recommendations for using drugs from the immunotherapy, VEGF, and mTOR groups. This review emphasizes seeing those guidelines within the context of other clinical issues. For the situation in which those other issues dominate the course of the disease, the clinician may adopt a

Table 2. — Selected Emerging Randomized Drug Trials

Clear Cell RCC With Measurable Disease		
Arms (acronym)	**Pretreatment**	**Conclusions**
Tivozanib vs sorafenib[15] (TIVO-1)	First-line	PFS of tivozanib better than sorafenib[16] OS not better than sorafenib[17]
After sunitinib: temsirolimus vs sorafenib (INTORSECT)	Second-line	PFS nonsignificantly favored temsirolimus OS significantly favored sorafenib[18]
Dovitinib vs sorafenib[19]	After one VEGF TKI and one mTOR	Completed accrual
Sorafenib → sunitinib vs Sunitinib → sorafenib Japan[20] Germany[21]	First-line	No data Comment: Several nonrandomized retrospective studies show little OS difference apparent, within the limitations of retrospective designs. An aggregated analysis favored sorafenib than sunitinib.[22]
Pazopanib vs sunitinib (COMPARZ)[23]	First-line	Pazopanib not inferior[23]
Everolimus → sunitinib vs sunitinib → everolimus[24] (RECORD-3)	First-line	Sunitinib → everolimus still favored[25]
Sunitinib ± IMA901 peptides vaccine[26]	First-line Only HLA-A2	Ongoing accrual
Sunitinib (and no nephrectomy) vs nephrectomy → sunitinib[27] (CARMENA)	First-line	Ongoing accrual
Nephrectomy à sunitinib vs sunitinib (× 3 cycles) → nephrectomy[28] (SURTIME)	First-line	Ongoing accrual
Adjuvant Studies After Nephrectomy (Neither Metastatic Disease nor Resected Metastases)		
Girentuximab vs placebo[29]	Clear cell only	No difference in DFS[30] Drug is an antibody to carbonic anhydrase IX protein, expressed by clear cell RCC
Sorafenib vs sunitinib vs placebo[31] (ASSURE)	Non–clear cell allowed, mostly clear cell	Accrual completed
Pazopanib vs placebo[32] (PROTECT)	Clear cell only	Ongoing accrual
Everolimus vs placebo[33] (EVEREST)	Non–clear cell allowed, mostly clear cell	Ongoing accrual
Vitespen vs placebo[34]	- Positive result for PFS in "no renal vein invasion" subset was basis for marketing approval in Russia - Not FDA approved or available	

FDA = US Food and Drug Administration, HLA-A2 = human leukocyte antigen-A2, mTOR = mammalian target of rapamycin, OS = overall survival, PFS = progression-free survival, DFS = disease-free survival, RCC = renal cell carcinoma, TKI = tyrosine-kinase inhibitor, VEGF = vascular endothelial growth factor.

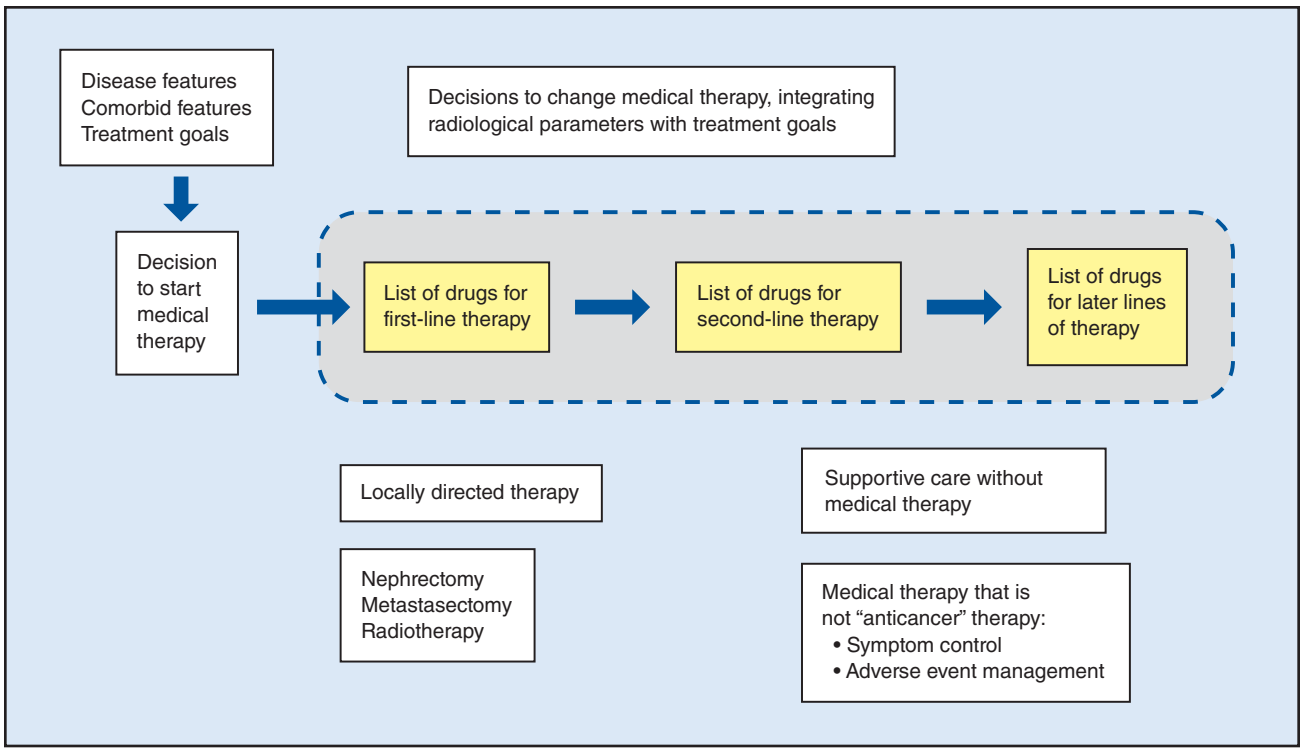

Fig 1. — Context for drug-choice guidelines.

more heuristic approach, working from the results of nonrandomized studies or other experiences. These decisions include debulking nephrectomy, metastasectomy and, for medical therapies, integrating adverse event experiences and time points for initiating medical therapy or changes in such therapy based on radiological findings as well as on their clinical context.

Medical Treatments

Among marketed immunotherapy approaches, interleukin 2 (IL-2) and interferon alfa have the longest in-depth experience. These are recombinant proteins with specific receptors on leukocytes and for interferon on other cell types, including vascular endothelium, that may have an antiangiogenic mechanism. These immunotherapies, as well as other investigational immunotherapies, work therapeutically by changing leukocyte behavior so as to cause the activation and production of other cytokines, and, consequently, the regression and suppression of tumor cells.[38] Randomized trials were performed on the subcutaneous administration of IL-2 and on inpatient high-dose schedules for kidney cancer[13,14]; the standard high-dose is distinguished by a characteristic pattern of adverse events, including fever, chills, and capillary leak, as well as some complete tumor regression of open-ended, unmaintained durability.[13,14,39]

The subcutaneous administration of interferon has a latency of several hours, usually before the onset of symptoms such as fever and chills. In a contemporary setting, the use of interferon as a single agent is rare due to the results of phase III randomized trials demonstrating that it was inferior to the interferon-only arms of sunitinib, bevacizumab with interferon, and temsirolimus.[3,5,6,11] The emergence of the lymphocyte protein programmed death-1 (PD-1) as a viable immunotherapy approach for kidney cancer with a low-intensity outpatient schedule is in active development.[40]

Rapamycin-related drugs are part of a group of compounds with a long history, including their use for the prevention of allograft organ rejection. Everolimus[12] and temsirolimus,[11] which is metabolized to sirolimus, target the function of the mTOR protein by binding the protein FKBP16, which leads to lower activity of the mTOR complex 1 (mTORC1). Although the mTORC1 should slow tumor growth, the noninhibition of the other mTOR complex, mTORC2, may lead to feedback upregulation of Akt levels, attenuating the net effect on the growth of cancer cells.[41] Newer investigational compounds, which are not rapamycin analogs, inhibit mTOR function and are in development.[42] Some theoretical basis to combine VEGF and mTOR inhibitors exists,[43] but this approach has had little practical impact and to this point shows little advantage over a sequential strategy.[44,45] In the future, the anticancer effect for newer drugs interacting with the mTOR axis may have more pronounced clinical responses than what is currently obtained with the rapamycin analogs.

Temsirolimus is administered at a fixed 25 mg, given once a week, with a high peak level, then a

second peak of sirolimus, an active metabolite.[11] In terms of pharmacokinetics, patients have a few days per week with very low blood levels. Neither efficacy nor adverse events of weekly compared with daily administration have been directly or comparatively studied in kidney cancer therapy. Everolimus therapy in kidney cancer was tested as an initial daily 10-mg oral uniform dose (with dose adjustments as needed to manage adverse events); when administered this way, the dose results in a more uniform, continuous blood level of the drug.[3]

Many drugs that inhibit the VEGF pathway have been developed and, in terms of pharmacodynamic targets, they may be the least uniform group.[46,47] Oral sorafenib[4] and sunitinib[3] were initially introduced to the market and approved by the FDA in 2005 and 2006, respectively, followed by the kidney cancer-directed FDA approval of intravenous bevacizumab[5,6] in combination with interferon in 2008, and then two more oral agents, pazopanib[7] and axitinib.[9] In 2012, a positive progression-free survival (PFS) phase III trial for oral tivozanib was reported[15]; the OS report was less distinctive.[17] An FDA evaluation is anticipated in July 2013; an open phase III trial compared dovitinib to sorafenib,[48] and other VEGF axis compounds are in extensive testing in non-kidney cancer indications, which are outside the scope of this discussion. Pharmacological effect notwithstanding, patient-to-patient variations of absorption and metabolism influence the pharmacodynamics of efficacy and adverse-event experiences. Efforts to manage adverse events can significantly impact tolerability and drug delivery.[49,50] Details of selected dosages and schedules are presented in Table 3.[3-17]

Debulking Nephrectomy

The population of patients with metastatic kidney cancer includes those with prior nephrectomy and later metastatic recurrence and those for whom debulking nephrectomy is the initial issue for clinical discussion. The superior survival of those with sequential nephrectomy and then interferon over those with interferon as initial therapy (generally with permanent deferral of nephrectomy) was key in establishing the concept that the bulk of a primary tumor could influence the disease course, even among patients without overt symptoms to justify its removal (independent of OS). As reported for the combined Southwest Oncology Group (SWOG) and European Organisation for Research and Treatment of Cancer (EORTC), the median OS advantage of 13.6 vs 7.8 months was observed[51] and was consistent within the two individual trials. The specific applicability of the experience was emphasized for patients who

Table 3. — Selected Drugs With Differing On-Label or Per-Randomized-Trial Schedules

Name	Schedule	Comments
Interferon alfa[5,6]	≤ 9 million U, subcutaneous, M-W-F	Many published variations
Interleukin 2[13,14]	600,000-720,000 IU/kg/dose (usually 600,000) Dose for 15 min intravenous infusion every 8 hr, up to 14-15 doses/course	Some published variations, notably subcutaneous administration
Everolimus[12]	10 mg orally daily	2.5 mg and 5 mg doses also available
Temsirolimus[11]	25 mg/dose weekly	On-label dose reductions
Sorafenib[4]	400 mg orally twice daily	200-mg pills Dose reductions or omissions for management of adverse events
Sunitinib[3]	50 mg orally daily, with 28 days on, 14 days off	12.5- and 25-mg pills also available Initial dose reduction usually to 37.5 mg Other schedules considered
Pazopanib[7,8]	800 mg orally daily	200-mg pills Dose reductions or omissions for management of adverse events
Axitinib[9,10]	Initially, 5 mg orally twice daily	1- and 5-mg pills Target dose adjusted based on blood pressure and adverse events, to 2, 3, 5, 7, or 10 mg orally twice daily
Bevacizumab[5,6]	10 mg/kg/dose, every 14 days	In combination with interferon (as above, per FDA label) Other schedules used in other on-label diagnoses
Tivozanib[15-17]	1.5 pg orally twice daily, 21 days on, 7 days off	Trial completed No FDA label (5/2013)
FDA = US Food and Drug Administration, M-W-F = Monday, Wednesday, Friday.		

were good candidates because they were generally fit and with good projected renal reserve. In contrast, data from more contemporary databases suggest that the median OS rate was shorter than what is seen in patients with metastatic renal cell carcinoma who have good risk features.[1,2] Although a predilection of benefit was not observed for a particular anatomical pattern of metastatic disease,[51] other analyses suggest those with the higher fractional reduction of tumor bulk (ie, large primary and small volume of metastasis) achieve the most benefit.[52,53] This was a nuance outside the specific primary end point of the trial, but contemporary treatment planning should consider it. A similar conclusion was reached in nonprospective analyses for patients in the targeted therapy era.[54]

Some patients with directly attributable problems, such as flank pain or hematuria, may occasionally benefit dramatically with symptom control after the early adoption of nephrectomy. Patients with laboratory abnormalities such as anemia, fever, and hypercalcemia may also benefit. However, the established impact of worse performance status, anemia, hypercalcemia, and nonresected tumor bulk on prognosis should be recognized. Careful review of the estimated outcomes is needed when symptoms and prognostic features could improve with debulking. An attempt to improve prognostic features by debulking has not been addressed in a prospective randomized format.

Other issues also color the interpretation of these current upfront data. In well-selected cases, a markedly increased, contemporary availability of less invasive laparoscopic techniques exists, or of lessening the decrement of renal reserve through partial nephrectomy or the strategic use of energy-ablative local techniques.[55,56] These approaches can be seen as widening the applicability of upfront nephrectomy as an initial approach with survival impact. Recent analyses emphasized an apparent but specific benefit for nephron-sparing and OS rates for partial nephrectomy in patients without metastatic disease,[57,58] so such a benefit may exist for those with metastatic disease, particularly if the metastatic disease is indolent. However, no consensus exists about selecting a surgical technique. Another issue is the use of immune-mediated drugs (eg, IL-2) or investigational immunotherapeutic drugs (eg, nivolumab [BMS936558][27]) as initial medical therapy.[40] Theoretically, debulking will quantitatively lower the impact of tumor-derived cytokines on relevant lymphoid or dendritic cell function, mediating a better environment for an anticancer effect.

Pivotal targeted-therapy trials are dominated with postnephrectomy patients.[59] Conversely, an appreciation of the morbidity of nephron loss and for the potential of the medically mediated control of the primary tumor may sometimes be used to defer upfront nephrectomy in favor of initially targeted drug therapy. Indeed, a single-arm study of patients with primary kidney tumors identified as technically unresectable found that, for 13 of the 30 patients, surgery became feasible with sunitinib treatment.[60] Similarly, the neoadjuvant use of bevacizumab was also feasible.[61] Response of the primary tumor size also has been identified as a favorable prognostic feature.[62] Together, these single-arm experiences and a variety of case reports of VEGF approaches[63,64] define a synthesis therapeutic pathway of debulking and targeted therapy.

Because the comorbidity spectrum is broad among patients faced with debulking nephrectomy, the reasons for deferring technically feasible nephrectomy may include medical therapy as well as issues of acute surgical risks or long-term risks of nephron loss.[65] In an ongoing French study, patients are randomized to nephrectomy and then sunitinib vs sunitinib without nephrectomy in patients with clear cell renal cell carcinoma with no prior medical or radiation therapy.[27] An EORTC trial[28] studied a similar population and excluded patients needing nephrectomy for symptom control; instead, the researchers randomized patients to immediate nephrectomy or delayed nephrectomy until three 6-week cycles of sunitinib therapy were completed. The results of these studies will be important contributions to possible recommendations about nephrectomy timing. As far as individualizing a recommendation, these and other experiences (drug selection, duration of presurgical treatment) may likely influence practice patterns. Some patients may defer definitive local treatment because of good response, while others may defer because of early systemic disease progression.

Nonmedical Treatments

Many anatomical patterns of kidney cancer metastasis exist. Of the groups of patients studied in the pivotal trials,[3-12] the patterns are generally consistent, with about 70% of patients having lung metastasis. Lymph node, bone, and liver are the next most common sites of metastasis. The biological basis for the differing patterns of spread currently remains poorly defined.

Regarding bone metastasis, some patients may have a fracture, or an impending fracture, with an absolute indication for initial local therapy, thus representing another situation systematically excluded from trials designed to have a homogeneous group receiving uninterrupted treatment with a single medical treatment. The exclusion of patients requiring concurrent radiation therapy is a usual criterion of drug treatment trials. In a real-world situation, a targeted therapy may be initiated and then possibly interrupted while an isolated lesion is locally and definitively treated. In some cases, the isolated lesion may represent a breakthrough, isolated progression

site. Contrary to most experience in pivotal trials, in my experience such a site could be treated definitively in the clinical setting and then the same medical therapy — which is still controlling other sites of disease — may be resumed.

If one or two metastatic sites are anatomically accessible, strategic resection or irradiation followed by an organized, cautious program of observation may yield a multiyear interval before another therapeutic maneuver is needed. Avoiding systemic medical treatment can be rewarding for patients by deferring or eliminating exposure to the risks of side effects and by prolonging disengagement from the financial costs and psychological burdens of active anticancer treatment. However, the feasibility of resection for some anatomical sites is marginal or prohibitive with regard to surgical or radiotherapy risk, while in others the pattern of spread of the cancer is ultimately more multifocal or rapid than originally assessed, so medical treatment is a key approach. A similar experience can be seen in treatment planning for metastasectomy preceded by neoadjuvant therapy.[66,67]

Fig 2 illustrates a case of a 49-year-old woman with a resectable dominant kidney tumor, (clear cell histology), and synchronous, unresectable liver metastasis at presentation. She was treated with VEGF-targeted therapy (sunitinib), resulting in observable downsizing of both lesions, with no new lesions. However, this approach did not improve the resectability of the liver lesion. She was treated with nephrectomy and irradiation of the liver lesion, then was off medical therapy. Later, a second small liver lesion was detected, so she was subsequently treated with yttrium-90 glass microsphere embolization. Although this anecdotal report is not meant to be as representative as a pivotal trial, it does illustrate an excellent outcome in which delayed nephrectomy, a limited course of neoadjuvant sunitinib (despite a resectable primary tumor), and embolization were associated with adequate disease control.

Brain metastases of kidney cancer may occur as relatively isolated lesions and not affect global function. Small lesions, particularly in the range or 2 cm or less,[68,69] can be considered for stereotactic radiosurgery, while surgical resection may be used with larger or hemorrhagic lesions. For many patients, particularly those with few lesions, definitive local control of the central nervous system can be achieved without full brain radiation. The issue of kidney cancer "radiation insensitivity" may be the basis of an advantage of stereotactic radiosurgery, where anatomically appropriate, rather than full brain radiotherapy, because the dose delivered to the tumor is higher, a logical approach in the setting of possible radiation resistance.

Patients with brain lesions have been systematically excluded from pivotal trial experiences, although data from some large databases, such as the US expanded access program for sorafenib[70] and for sunitinib,[71] reveal that OS patterns (in treatments incor-

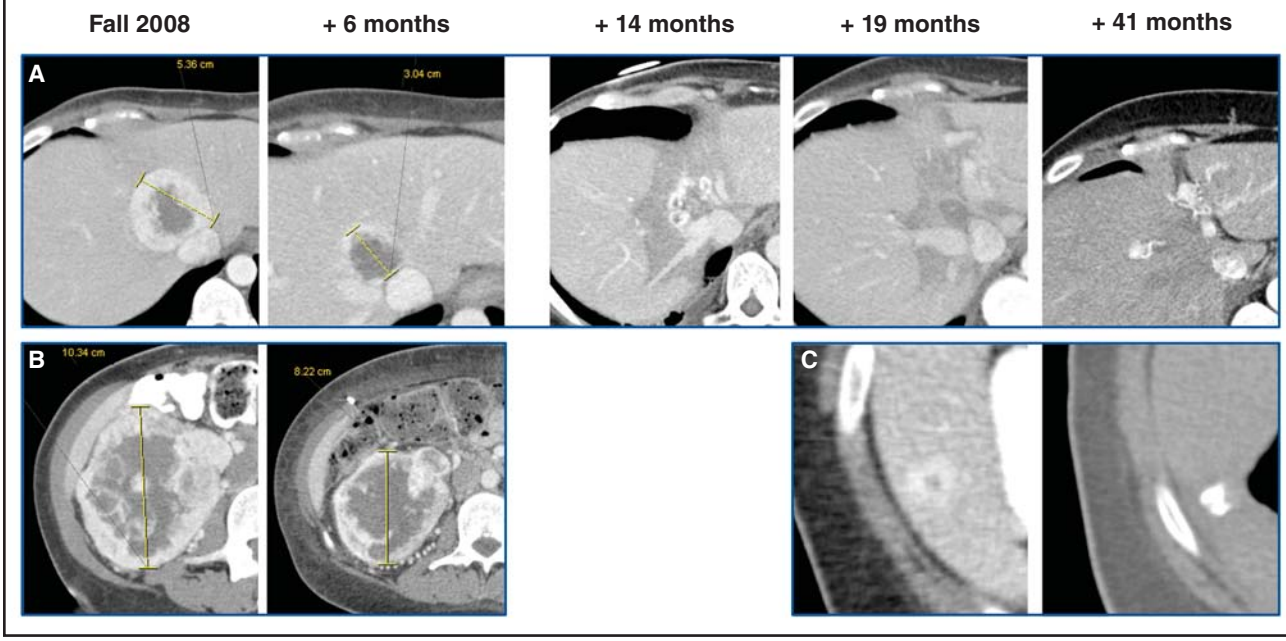

Fig 2A-C. — Fall 2008: presentation with (A) a 5-cm metastasis and (B) a 10-cm kidney mass in the liver. At 6 months (sunitinib therapy): regression of the kidney mass to 8 cm and the liver mass to 3 cm, with significantly more necrotic appearance. Nephrectomy showed Fuhrman grade 2 clear cell renal cell carcinoma. After surgery, the liver mass was marked with ethiodized oil I-131 injection and treated with 5 consecutive fractions of radiotherapy at 1,000 cGy. At 14, 19, and 41 months: radiation changes and dissipation of the marker are seen on subsequent imaging. At 19 months (C): a small, 1-cm additional lesion is seen in the liver (with intravenous contrast). At 41 months, the patient was treated with segmental yttrium-90 embolization (no intravenous contrast, showing calcification), and remained off therapy with no other progression from the original presentation (35 months from end of sunitinib treatment).

porating local treatment of the brain metastasis) are similar for the cohorts without or with that particular anatomic pattern of cancer spread. Medical therapy without localized treatment of brain metastasis was not effective in one phase II study of sunitinib in patients with renal cell carcinoma.[72] An approach that is meant to be definitive for the particular anatomic site of the brain lesions should be used.

Some cases of metastatic kidney cancer may show a slow growth rate, with isolated cases recurring more than a decade after initial presentation. However, this latency should not be automatically presumed to indicate whether a slow growth rate will indefinitely persist. In my experience, in such a situation in which immediate treatment is unnecessary, an individually tailored schedule of interval re-evaluations should be planned once metastatic kidney cancer is anatomically evident, even if it appears to have small volume. For pivotal drug trials with a placebo arm and then a crossover at progression (everolimus[12] and pazopanib[7]), it was uniformly observed — in groups of patients with a more directly evident need for starting new treatment — that average OS differences were less than the median delay of treatment initiation, which was a couple of months. A similar phenomenon was observed during trials with an active comparator arm, bevacizumab[5,6,73] and axitinib,[10] that studied a deferral of "change of therapy," not "start of therapy." That scale of interval can rationally be used for planning surveillance, but no empirically derived interval can be recommended. Although it is not an indefinite reprieve, an interval of a few months generally appears to have little OS impact in most cases.

Comorbid Bases for Medical Deferral

Besides anatomical and histological variability, patients with stage IV kidney cancer may have a wide range of comorbidities and tumor growth rates. For example, a wide range of OS patterns have been observed, even within a single prognostic group, such as the good-risk patients comprising about 20% of the group described in an early discussion of prognostic factors.[1] By about 7 months, 20% of the group had died, but 20% were still alive at 4.5 years. Potential study participants seeking medical therapy for one reason or another are usually not in urgent need for nonmedical (locally directed) treatments. The applicability of the trial results for patients seeking treatment because of psychological or nonmedical reasons may be different.

Examples of medically manageable, well-compensated, long-term comorbidities that are systematically depleted from pivotal trials include moderate renal dysfunction (eg, creatinine level of 2 mg/dL), recent myocardial infarction (eg, stent placement and minimal near-term risk of acute coronary syndrome), and compensated congestive heart failure.[3-10] Exclusion of this often-encountered patient population from trials is an absence of direct experience, which is not the same as observation of adverse experience and is not an automatic basis for avoiding targeted therapies as part of a successful treatment plan for these individuals. Another example is the practical treatment of patients with renal cell carcinoma on hemodialysis.[74,75]

Appropriate attention to supportive care should be balanced with anticancer efforts. For example, one would consider an increased frequency of cardiac evaluations for individuals with cardiac disease risk factors or of diabetes medicine adjustments for participants taking mTOR inhibitor drugs. This is particularly of concern for patients with disease features suggesting a relatively slower growth pattern than that studied in the trial but who have anxiety related to an incidentally detected, asymptomatic metastasis of an unknown growth rate. For heuristically selected cases, a few months of observation without treatment may result in a qualitative difference of the estimated risk-benefit balance and could heavily influence the timing of treatment initiation.

Treatment Through Nominal Progression

A necessary feature to the designs of pivotal trials is to apply a uniform criterion for end point definitions. For trials in which the primary end point is PFS, there must be a way for patients in the control arm (an arm that may incorporate a placebo) to discontinue treatment. However, some arbitrary elements do exist: percentage thresholds for the definition of the progression of slowly increasing lesions (typically 20% more than the best value for the sum of linear dimensions of the dominant lesions, in Response Evaluation Criteria in Solid Tumors [RECIST] 1.0 or 1.1) mean that participants with slightly different percentage changes (eg, 18% vs 22%) would be directed to different treatment plans. Similarly, a patient may have several well-controlled lesions, such as lung nodules, when an isolated, anatomically solitary area, such as a brain metastasis or bone metastasis, is identified. Although no doubt exists that this meets the trial-applied definition of progressive disease, in clinical practice, it is a separate question as to whether it is of overall clinical benefit to keep patients on the same treatment and use a locally definitive procedure to control those breakthrough lesions. Some individuals may not have previously tolerated other drugs and may not want to change from a well-tolerated treatment to one with several unknown issues, with regard to response and to possible tolerability issues.

A particular issue surrounding clear cell kidney cancer therapy with VEGF-axis drugs involves exactly which rules apply to disease progression. As proposed by Choi et al,[76] some radiological changes of cancer may demonstrate a response (onset of necrotic, non-

enhancing appearance) while paradoxically increasing the size on the CT scan slice image. Applying different rules can dramatically alter the assessment of a treatment time point as meeting clinically relevant criteria, thus compelling a recommendation to change treatment. For example, a change of treatment resulted in 49 (Choi criteria) vs 11 (RECIST criteria) partial response events in a group of 155 patients analyzed.[77]

Initial Therapy

Can a series of disconnected randomized trials with PFS end points define optimal initial therapy and also be optimized to an OS end point? Mostly attributable to crossover events, the OS differences are generally favorable for the investigational arm, but they are smaller and, in some cases, not significant.[3-6,8,10] As suggested in Table 1, smaller differences in median OS compared with differences of PFS are the rule for the randomized VEGF trials, and this was also observed in the everolimus vs placebo trial.[12] For patients starting medical therapy, a single answer to the question of which drug to pick may not even exist. Crossover responses are observed within the experiences of changing from any one drug to almost any other one for several VEGF-axis drugs; prior therapy with one drug may end with intolerance or an idiosyncratic low blood level related to population heterogeneities of absorption or metabolism.

IL-2 immunotherapy has been used as a treatment option for nearly 20 years, but there has been a slow evolution of recommendations for patient selection. The use of the drug as an inpatient, high-dose, first-line treatment is associated with the distinctive feature of durability, particularly in those with complete responses. For some patients for whom there is no clear selection algorithm, upfront VEGF-type therapy should be deferred so that the immunological approach can be used as initial therapy.

A retrospective study[78] describing an excess of cardiac morbidity and no responses among 23 patients previously treated with sunitinib, sorafenib, and bevacizumab did not biologically define the basis for immunotherapy resistance when treated with IL-2. However, it reinforces that, among off-study available medical therapies, IL-2 is usually more appropriate to be sequenced upfront than immediately after progression through a VEGF drug treatment.

The absence of features such as young age, fitness by cardiac, pulmonary, and renal assessments, clear cell type, normocalcemia and normal hemoglobin, or slower apparent growth rate are generally used to define patients for whom IL-2 treatment will not be used. Conversely, good responses seen in a small percentage of patients will continue to drive interest in this treatment. Results from randomized trials of high- and low-dose IL-2 suggest that most anatomical sites of disease revealed complete responses.[13,14] Currently, however, in the absence of quantitative assays of immunological metrics of tumor features to define a better group, a key decision for the initial medical evaluation of a patient should involve deciding how to pursue initial medical therapy for metastatic disease with IL-2.

Conclusions

Medical decision models vary. At one extreme are models for medical decisions composed of guidelines closely echoing pharmaceutical registration trials, with rigid entrance criteria and predefined end points meeting strict criteria level 1, randomized trial-based evidence.[18] These are devoid of subset analyses or secondary end points, carrying a mathematically higher opportunity for false conclusions. Although ranked or unranked lists and algorithms of licensed drugs are legitimately described as being based on evidence, these lists still rely on the assumptions of similarity to the trial population and to the treatment choices within the treatment plan of the trial. These assumptions have limited validity for many patients, particularly those with kidney cancer in which the "average patient" of trial experience is different from the patient actually being treated. These differences should be highlighted by the treating physician as much as the positive primary end points themselves. At the other extreme of the medical decision process could be a view that "everyone is different" — that is to say that there are not enough data specific to a particular patient's exact situation to make a definite recommendation. This could lead one to emphasize anecdotal experience over randomized trial results. The practical application of kidney cancer therapy must lie somewhere between those perspectives. Although some pearls or practice patterns can be tested in an appropriate prospective randomized trial format (eg, initial vs deferred nephrectomy), the economical or medical hurdles for accomplishing subset-directed studies for kidney cancer are not likely to be overcome. Level 1 evidence directed at some important details and decision points may never exist. However, persistent gaps in the empirical data relating to comorbid features of the patient at hand should not lead to arbitrary decisions.

Locally directed therapies that encompass conventional surgery, external beam radiation, stereotactic radiosurgery, or other technique may be associated with remissions of significant or lifelong durability. The process of selecting patients for this type of locally directed nonsystemic treatment is not addressed by randomized trials of medical therapy.

Metastatic tumor burdens of kidney cancer remain heterogeneous, whether measured by histological, anatomical, or chronological terms. Until biological

assays are sufficiently robust to demonstrate effects above the therapeutic results observed in randomized clinical trials that aggregate patients together in many ways, the overall disease management that encompasses a multidisciplinary approach rather than a simple question of drug choice will dominate the optimization of patient outcomes. To this end, clinicians must work with the randomized trial data of the immunotherapy, mammalian target of rapamycin (mTOR), and vascular endothelial growth factor (VEGF) pathway drugs, making do with extrapolations and secondary end points informing on the relative frequencies of adverse events or pharmacokinetic differences. Similarly, data on nephrectomy and metastasectomy must be part of an individualized decision and coordinated with specialties of interventional radiology, diverse surgical specialties, and radiation oncology. As new drugs are introduced to the market, a further nuanced selection of drugs and non-drug therapies will become possible. However, the algorithms of drug selection remain embedded in an informed understanding of the differences to tailor a multidisciplinary treatment plan for the needs of patients with kidney cancer.

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