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Sunitinib in Special Situations in their Daily Practice

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Abstract

In the last decade, we have witnessed a change in the therapeutic management of patients with advanced kidney cancer. Systemic treatment of advanced Renal Cell Cancer (RCC) has been revolutionized by targeted therapy with drugs that block angiogenesis unfortunately; these studies are not always the reality of the practice of medical oncology at the inquiry reflected everyday and see how many subgroups of patients are not represented appropriately. Many patients with RCC do not meet inclusion criteria. For instance, more than 40% of patients with metastatic RCC are in special situations, i.e. elderly patients, bone metastases, hepatic impairment, type 1 and 2 diabetes, renal insufficiency and end-stage renal disease , haemodialysis , brain metastases, and unresectable surgery. These patients are poorly represented in trials. Little is known about the activity of targeted therapies, such of sunitinib, in these subsets of patients. It could be a benefit of sunitinib treatment for these patients, with good tolerance, by personalizing treatment in each situation. In this article, we review the use of sunitinib in these real practice patients and its specials situations.

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Introduction

Systemic treatment of advanced RCC has been revolutionized by targeted therapy with drugs that block angiogenesis. Vascular endothelial growth factor receptors and their ligands play important roles in tumour growth and angiogenesis.

Sunitinib, an oral multitargeted tyrosine kinase inhibitor with an antiangiogenic and anti -tumor properties, inhibits VEGFR, PDGFR, FLT3, KIT and RET was approved for the treatment of advanced renal cell carcinoma since 2006.

A commonly asked question is whether patients with metastatic RCC (mRCC) in clinical trials are representative of the general population for this disease. Many patients with mRCC do not meet inclusion criteria, particularly those with a poorer prognosis. For instance, more than 40% of patients with mRCC are in special situations, i.e. elderly patients, bone metastases, hepatic impairment, type 1 and 2 diabetes, renal insufficiency and end-stage renal disease , haemodialysis , brain metastases, and unresectable surgery. These patients can have an extremely short life expectancy, and are poorly represented in trials and they are often excluded from clinical TKIs therapy. This little is known about the activity of targeted therapies, such of sunitinib, in these subsets of patients.

There have shown the efficacy of sunitinib in a broad mRCC population, particularly in subgroups who might be predicted to tolerate therapy less well than patients in well-defined, selected populations in the clinical phase II and III trials. Furthermore, there have shown that the safety profile of sunitinib is very similar for these poor-prognosis groups to that reported in well-defined patients populations [1-191].

Elderly Patients

Generally, elderly patients are no well represented in clinical trials, but in the case of sunitinib phase III trial, 250 patients of 750, were 65 years old or older; and the benefit achieved was similar to those younger [1].

At the expanded access program trial were included 1418 (32% of the total) patients over 65 years old. In this subgroup, a response rate of 17% was achieved (it should be noted that in this study the response evaluation was not mandatory, which may explain the low percentage of responses), progression-free survival (PFS) of 11.3 months (95% CI 10.7-12.3) and an overall survival (OS) of 18.2 months (95% CI 16.6-19.8), which were similar to those of the overall study population (PFS 10.9 months, OS 18.4 months) [2].

Despite the usual limitations, retrospective study in unselected patients treated with sunitinib, indicate that patients ≥70 years of age considered fit for the standards regimen by their medical oncologist had a poorer safety and efficacy profile compared with younger patients such as those enrolled in clinical trials [3,4]. However, patients who were given an adapted regimen because of their delicacy health experienced a better tolerance leading to a similar rate of early discontinuation because of therapy-related adverse events [3]. The response rates, Os and PFS did not differ significantly between the standard regimen (sunitinib 50 mg/day for 4 weeks on/2weeks off) and the adapted regimen (sunitinib 37.5 mg/day for 4 weeks on/2weeks off) groups [3,4].

Other smaller studies have also shown similar efficacy between patients younger and older than 70 years. In a recent study published by Hutson et al. [5] data from 1059 patients enrolled in 6 clinical trials were analyzed, and the data of PFS and OS were compared using log-rank test in the population less than 70 years (n=857) vs. 70 years or older (n=202). In the overall population trend it was found to better PFS in the group of older patients (10.9 vs. 9 months; HR 0.85, 95% CI 0.70-1.02, p=0.0830), data that are similar to a study with sorafenib [6], raising the possibility that elderly patients with RCC may be more responsive to anti-angiogenic therapy. In patients who were treated with sunitinib in first line (n=783, 74%) PFS was comparable between the 2 subgroups of patients, 9.9 vs. 11 months, respectively (HR 0.89; 95% CI 0.73-1.09; p=0.2629) and OS 23.6 vs. 25.6 (HR 0.93, 95% CI 0.74-1.18, p=0.3350), and the same happened in the context of cytokines after treatment.

A recent RCC tumor biopsy study revealed age-related differences in tumor vasculature, in which clear cell RCC tumors from patients aged ≥65 years had significantly higher micro vascular density than those from patients aged <65 years, and markers of angiogenic activity also differed [7].

Khambati et al. [8] published retrospective data from over 1300 patients treated with anti-VEGF therapies mRCC in the International Database Consortium, finding a 10.4% of patients 75 years or older (n = 144), of which 98 had received sunitinib as first-line. It did not show significant differences in OS in both groups. Furthermore, when adjusted by known poor prognostic factors [9], the hazard ratio for age 75 years and older was not found to be associated with poorer OS or shorter treatment duration.

In the other hand, data of Surveillance, Epidemiology, and End Results (SEER) suggest that survival in patients >75 years is inferior to the younger and do not have a better survival in the era of targeted therapies (2005-2009) regarding the age of cytokines (1992-2004) [10]. But, in this study comorbidity or the type of treatment used is not contemplated, which could influence the results.

With respect to toxicity in this patient group, Hutson et al. [5] found that some side effects were less frequent in younger patients, including fatigue (60 vs. 69%), cough (20 vs. 29%), edema (17 vs. 27%), anemia (18 vs. 25%), decreased appetite (13 vs. 29%) and thrombocytopenia (16 vs. 25%) [5]. Younger patients were more likely to have a highest grade adverse effects of grade 1 or 2, and older patients more likely to have a highest grade adverse effects of grade 3, possibly due to more comorbidities in this population [11,12]. Recently Jang et al. [13] published the results of an analysis of cardiovascular toxicity after antiangiogenic therapy in patients older than 65 years with renal cell carcinoma at the SEER database trial; 670 patients who received sunitinib or sorafenib were identified and they found a risk for stroke with a hazard ratio (HR) of 2.28 for sunitinib (1-5.22) and 5.30 for sorafenib (1.8-15.6).

There are data suggesting that older adults may be more prone to discontinue therapy as a consequence of toxicity as opposed to disease progression [14].

In the retrospective study of De Giorgi et al. [3] data of 185 patients were analyzed founding that there was a greater need for dose reduction or schema's changing in the group of patients of >70 years, but this did not affect PFS (11 months) or OS (25.5 months).

The efficacy profile of sunitinib appears comparable in older and younger patients with advanced RCC, with some limited differences in the safety profiles, that require lower doses more often without a reduce in effectiveness.

Brain Metastases

The management of brain metastases from mRCC has not been defined and must be do it on individual basis. Patient selection, and the type of treatment chosen, has been shown to greatly influence outcome in patients, when undergoing single fraction-radiosurgery or multiple fractions-fractionated stereotactic radiosurgery (SRS) of brain metastases.

In 1997, Gaspar et al. [15] reviewed patient characteristics and treatment variables of three Radiation Oncology Treatment Group Trials. A total of 1200 patients, were evaluable, and three prognostic groups were identified (Table 1), using the recursive partitioning analysis (RPA). Considering these factors, the usual therapeutic approach of brain metastases is local treatment, surgery or SRS with or without whole brain irradiation (WBRT).

Surgical management of brain metastases from RCC has been investigated in three retrospective studies with a median survival ranging from 14.5 to 23 months (16-18).

SRS has emerged as an alternative option, combining the potential for definitive local control with a favorable adverse effect profile and could be repeated in case of progression [19]. OS patients undergoing monotherapy with SRS stratified by RPA class has been: 18-24, 8.5-9.2, and 5.3-7.5 months for classes 1,2 and 3 respectively, with a local control rate of 94% [20-22].

RCC has traditionally been considered a radioresistant tumor.

Table 1: Prognostic classes and associated survival in patients undergoing local treatment for brain metastases.

Class	Prognostic factors	Survival, median in months
I	PS>70 Age <65 years Controlled primary tumor No extracranial metastases	7.1
II	All other patients	4.2
III	PS <70	2.3

PS=Performance Status

Because of the modest response of RCC BM to WBRT alone and the low benefit in survival it is usually not an option for these patients [23,24].

Studies in animals have shown that brain penetration of sunitinib may reach 31%, a significantly higher penetration than that achieved with other TKI, which ranges from 1 to 10% [25]. However, Dudek et al. [26] have shown that transportation of sorafenib and sunitinib across the intact blood-brain barrier was restricted, although the incidence of brain metastases per unit time is decreased in patients on TKI era in comparison to the cytokine era.

Patients with BM are usually excluded from all phase III randomized clinical trials, and clinical data on the effectiveness of TKIs against RCC BM are limited [27]. The efficacy of sunitinib for the treatment of BM, same of other factors of poor prognosis, remain unknown until results from the open-label, Expanded Access Program (EAP) were published by Gore et al. [2]. In this EAP, of 321 patients with BM included, 213 were evaluable for tumour response. No data was given regarding prior Central nervous system (CNS) irradiation. Patients received a median of 3 cycles of treatment compared to 6 cycles in the overall population. Rates of dose modification and discontinuation of therapy were also similar. The safety profile of sunitinib in the BM subgroup was similar to the overall population, although the incidence of treatment-related AEs was lower; this may be due to a shorter drug exposure. The most common AEs were diarrhea (34%), fatigue (32%), nausea (29%), and mucosal inflamation (27%). The most common grade 3/4 AEs were fatigue and asthenia (both 7%), thrombocytopenia (6%), neutropenia (5%), anemia (4%), and hand-foot syndrome (4%), and only one patient developed a cerebral hemorrhage. The efficacy analysis of sunitinib in this subgroup of patients found that 111 patients (52%) reported stable disease (SD) for 3 months, 1 patient had a complete response (CR), and 25 patients (12%) had a partial response (PR). Median PFS and OS in patients with BM was 5.6 months (95% CI: 5.2-6.1), and 9.2 months (95% CI: 7.8-10.9), respectively, whereas median PFS and OS for the overall population was 10.9 months (95% CI: 10.3-11.2) and 18.4 months (95% CI: 17.4-19.2) respectively (Table 2).

Several case reports [28-31] and retrospective series [32-34] of RCC with BM have been published reporting the efficacy of sunitinib in this setting and include cases with durable CR. Of these, highlight the study published by Verma et al. [34]. They compared the outcome in 41 patients from the pre-TKI era with 40 patients who received TKI; their results suggest that TKIs are associated with a trend of improvement in OS, but no significant improvement in local control (LC) of BM.

The results from a phase II trial of sunitinib in patients with RCC and untreated BM have been recently published [35]. The primary end point was objective response rate in BM after 2 cycles of treatment. In terms of efficacy, the outcome was not encouraging and stabilization disease was the best response achieved, it was seen in 5 patients (31%). Median time to progression was 2.3 months (95% CI: 1.2-5.4); and median OS was 6.3 months (95% CI: 2.1-7.9). Sunitinib appears to have an acceptable toxicity profile in patients with untreated BM from RCC. The authors suggest that sunitinib might be less present in brain than previously thought; a poor penetration or an increased drug metabolism because of the effect of inducers, such as glucocorticoids, might be part of the explanation.

Optimal treatment for brain metastasis remains a significant unmet therapeutic need. Data for the use of targeted therapies in patients with BM is limited because of the exclusion of these patients from large trials, due to the perceiving risk of intracranial bleed and the desire of including only patients with a better life expectancy. However, clinical experience suggest that sunitinib may be a good treatment option for patients with BM from RCC and its safety profile is comparable to that of the overall population of patients with RCC.

Table 2: Summary of efficacy results of the EAP with sunitinib.

	Overall population (N= 4371)	Brain metastases (N=321)
Number of evaluable patients	3464	213
OR CR PR	603 (17%) 34 (1%) 569 (16%)	26 (12%) 1 (<1%) 25 (12%)
SD	2029 (59%)	111 (52%)
PFS, months (95% CI)	10.9 (10.3-11.2)	5.6 (5.2-6.1)
OS, months (95% CI)	18.4 (17.4-19.2)	9.2 (7.8-10.9)

OR: Objective Response; CR: Complete Response; PR: Partial Response; SD: Stable disease; PFS: Progression Free Survival; OS: Overall Survival

Bone Metastases

Approximately 1/3 of patients with mRCC have bone metastases [36], the skeleton is a common metastatic site, after the lung, with estimates of frequency ranging from 24% to 51% [37-39] , and these patients are at risk of skeletal-related events, including pain, pathologic fractures, spinal cord compression, surgery to bone, and occasionally hypercalcemia [40].

In a recent analysis the presence of baseline bone metastases was 28% [41], which is consistent with rates previously described [42,43]. The rate of skeletal-related events in patients with bone metastases was 6.4%, which is lower than previously reported rates. In the cytokine era, when therapies for mRCC were limited, rates of skeletal-related events in patients with bone metastases were >74% [44]. The skeletal-related events rate in patients with bone metastases secondary to mRCC in the targeted era is largely unknown.

Bone metastases are often associated with disseminated disease, most frequently affecting the axial skeleton with osteolytic lesions where bone resorption dominates over new bone formation [45].

In screened records of more than 1800 patients who died from RCC, 22% had bone metastases. They showed that the majority of patients with bone metastases at the time of RCC diagnosis were classified as poor risk according to MSKCC criteria, while most of good and intermediate risk patients developed bone metastases after respectively, 24 and 5 months. Almost 70% of RCC patients with bone metastases experience at least one skeletal-related event [46]. The probability to develop bone metastases in RCC patients parallels with increased survival related to the introduction of biological therapies.

As mentioned before, several studies suggest that the presence of bone metastases is associated with poor prognosis even worse than the prognosis of patients with liver metastases [47,48]. Bone metastases are usually related to a more aggressive subtype of disease as suggested by the higher percentage of patients with metastases or Fuhrman grade 4 at the initial diagnosis, the shorter median time between nephrectomy and diagnosis of metastatic disease and the greater number of metastatic sites at the diagnosis [49]. However, long survival in patients with bone metastases from RCC is not a rare event. This may be partially explained by data on tumor biological heterogeneity [50], although other factors may affect the

natural history of bone metastases in RCC population. Some authors suggest that bone metastases may have also a predictive significance, particularly with anti- VEGF-targeted therapy [51-53].

The presence of bone metastases was associated with shorter OS (13.2 vs. 20.2 mo) and shorter PFS (5.1 vs. 6.7 mo) when compared with patients without bone metastases [41] and was an independent factor for worse OS in patients treated with targeted therapy; a similar, but less pronounced, trend was observed for PFS [54].

The number of bone metastases was associated neither with the number of skeletal-related events nor with OS. No significant differences in terms of OS were found when comparing patients presenting with visceral metastases as first metastatic sites with those with bone metastases as first metastatic site.

Outcomes of patients with mRCC have improved dramatically since 2005, when agents targeting the vascular endothelial growth factor and mammalian target of rapamycin pathways were introduced [47].

Bone metastases from renal cell carcinoma are difficult to manage. They tend to be large, highly destructive, and hyper vascular tumors. They tend to be more resistant to systemic therapies than other metastases. In a performed a retrospective review of bone metastases of renal cell carcinoma to the extremities and pelvis; in patients who had all undergone surgery [55], local control is an important issue for patients with the potential for a long period of survival. Wide resection of bone metastases was an independent predictor of survival in patients with renal cell carcinoma [56]. Several authors reported that spinal metastasis was defined as a significant risk factor in patient survival [57,58] and one reason for the poorer prognosis was the difficulty of wide resection of the vertebral lesions [59].

Although the management of patients with bone metastases has been markedly improved by the introduction of bone-directed targeted therapies, their prognosis is still dismal, with a mean survival of 12 months [60,61]. The lower rate of skeletal-related events documented in this era could be explained by the improved efficacy of targeted agents. There are demonstrated that sunitinib prevented the growth of renal cell carcinoma cells in a bone metastatic mouse model and caused significant declines in bone turnover markers in patients treated with sunitinib [62].

In the era of targeted therapy an overall comparison between two TKI (including both first- and second-line treatment), sunitinib was associated with a longer mean time to progression of pre-existing metastatic bone lesions, which was close to reaching significance. With respect to new metastatic bone lesions (including both first- and second-line treatment), sunitinib was found to significantly prolong mean time to occurrence.

In patients receiving first-line treatment, new metastatic lesions occurred in similar number of patients treated with sunitinib and, although not statistically significant, sunitinib appeared to prolong the mean time to occurrence of new lesions. Similar results were observed in patients with preexisting lesions. Although statistically not significant, both sunitinib and sorafenib prolonged mean time to progression of pre-existing bone metastases. Similarly, combining a targeted agent such as sunitinib with radiation therapy may result in radio sensitisation or increase sensitivity to the inhibitory effects of the targeted agent [63-65].

In the pivotal Phase III study of sunitinib versus interferon - alpha (IFN - α), 30 % of patients in each arm had bone metastases [1]. In the baseline OS analysis, a greater benefit of sunitinib on IFN - α was shown, regardless of the location of metastases (bone, lung and liver) and the number of metastatic sites (1 vs. ≥2). Additionally, the presence of bone metastases is a prognostic factor with sunitinib OS (HR=1.462; 95% CI: 1077-1968; p=0.015 HR <1 risk reduction in favor of the absence of bone metastases.) and INF - α (HR=1.632 95% CI: 1198-2225; p=0.002) [66].

In a retrospective analysis of prognostic factors in mRCC, data from 1059 patients treated with sunitinib in first (74%) and second line (26%) at six clinical trials were analyzed. 29% of patients had bone metastases. The presence of bone metastases was associated, in multivariate analysis, with worse OS (16.1 vs. 27.8 months; HR 1.535, 95% CI: 1250-1886; p <0.0001), and in a subset of 215 patients (long-responders sunitinib with median OS of at least 30 months), the presence of bone metastases was independent prognostic factor associated with a lower overall survival (42.7 vs. 54.5 months; HR 2.337, 95% CI: 1275-4285; p = 0.0061). Additionally, in a retrospective study in which 223 patients treated with sunitinib in 4 centers are analyzed, the presence of bone metastases was associated again with a worse PFS (median 8.2 vs. 19.1 months, p <0.0001) and worse OS (median 19.5 vs. 38.5 months; p <0.0001) compared with the absence of these [47].

Bone metastases are a frequent problem in the patient with renal cancer and several studies, point to make it a poor prognostic factor. Treatment with sunitinib was found to reduce the incidence of new metastatic bone lesions and significantly to prolong the mean time to occurrence of new lesions.

Hemodialysis

There are currently few published data available on the use of TKIs in patients receiving hemodialysis (HD) [67-76]. Owing to the very limited number of cases reported in the literature, it is impossible to make any definitive conclusions regarding the tolerability and efficacy of TKIs in patients with mRCC receiving HD. Nevertheless, the activity of sunitinib and sorafenib that we have observed in this cohort of patients, is similar to that observed in patients with normal renal function in phase III trials (disease control: sunitinib 75% vs. 79%) [1].

It is well known that the prevalence of RCC in dialysis patients is much higher than in the general population. RCC patients may undergo hemodialysis owing to decreased renal function due to chronic kidney disease other than RCC. In addition, it is not uncommon for RCC patients to undergo nephrectomy; this results in a number of patients being dialyzed [77,78]. Although there is a close connection between RCC and dialysis, clinical trials that demonstrated the efficacy of the new drugs did not include patients with renal failure. Consequently, a consensus or clinical guidelines have not yet been established for sunitinib administration in dialyzed patients.

Long term dialysis is a risk factor for renal cell carcinoma (RCC) since the prevalence of RCC in hemodialysis or renal transplant patients is 40 to 100 times higher than that of the general population. The kidney and urinary tract organs are susceptible to systemic carcinogenic effects extending from biochemical and immunologic changes that occur with renal pathologies, resulting in loss of proper renal function [77,79,80].

Table 3: Sunitinib different schedules.

Classic-traditional schedule	Sunitinib 50 mg oral per day 4 weeks on /2 weeks off
Continuous daily dose.	Sunitinib 37.5 mg oral per day continuous
Biweekly schedule	Sunitinib 50 mg oral per day 2 weeks on /1 week off
Sunitinib-free interval regimen	Stop sunitinib at the time of maximal response and reintroduce it at progression
Other schedules	Starting on Monday, 1 tablet/day for 5 consecutive days a week (days 6 and 7 off therapy) for 5 weeks and 1 tablet/day on days 1, 3 and 5 in the sixth week (days 2, 4, 6 and 7 off therapy) until disease progression

Although a high interpatient variability have been observed in sunitinib concentrations and clearance, the plasma concentration of sunitinib is not significantly modified by hemodialysis, and the values of the extraction coefficient (E%) and hemodialysis clearance (CH_{HD}, mL/min) are all 0% and 0 ml/min in patients, which reflects that PK are not altered by hemodialysis; therefore, sunitinib can be administered at any time regardless of the timing of hemodialysis.

Case reports have shown the feasibility of using sunitinib in patients with severe renal impairment [81] (defined as an eGFR <30 mL/min/1.73 m^2) or on hemodialysis [67,76] but the pharmacokinetic data for sunitinib in patients on hemodialysis is inconsistent [82]. Investigated the steady-state pharmacokinetics of sunitinib in two patients treated with 50 mg sunitinib daily, for 4 out of every 6 weeks while on hemodialysis. They concluded that hemodialysis did not significantly modify the plasma concentrations of sunitinib or its active metabolite SU12662, based on their comparable arterial and venous concentrations 2h after the start of hemodialysis. However, the pharmacokinetic parameters, including the area under the plasma concentration-time curve and maximum plasma concentration, showed a 10-fold difference between the two patients, and were not in the range reported for patients with normal renal function [83]. Recently published a phase I open-label study evaluating the effects of severe renal impairment (creatinine clearance <30 mL/min) and hemodialysis on the pharmacokinetics and safety of a single 50 mg dose of sunitinib. They also concluded that the clearance of sunitinib and its active metabolite SU12662 was similar in patients with severely impaired renal function or on hemodialysis, when compared with patients with normal renal function, although plasma exposure to sunitinib and SU12662 was significantly lower in subjects requiring hemodialysis compared with those with normal renal function.

The pivotal phase III study that led to the approval of sunitinib in advanced RCC excluded patients with a serum creatinine concentration ≥1.5 times the upper limit of normal, and the expanded-access trial of sunitinib excluded patients with a serum creatinine concentration >2.0 times the upper limit of normal [2]; therefore, data regarding the efficacy and tolerability of sunitinib in patients with renal impairment are limited. Recently, a phase I open-label study evaluating the effects of severe renal impairment (creatinine clearance <30 mL/min) and HD on the pharmacokinetics and safety of a single 50 mg dose of sunitinib has been published. The clearance of sunitinib and SU12662 was similar in patients with severely impaired renal function, or undergoing HD, to that in patients with normal renal function, although plasma exposure to sunitinib and SU12662 was significantly lower in subjects requiring HD than in those with normal renal function [84].

Published data suggest that patients with severe renal impairment or end-stage renal disease on hemodialysis can be safely treated with sunitinib at doses of 25-50 mg daily for 4 weeks followed by a 2-week break. The observed efficacy and toxicity of therapy is similar to that reported in patients with normal renal function.

Pharmacokinetics

A recent phase I open-label parallel-group study, which included eight patients receiving HD, found that plasma exposure to sunitinib and its active metabolite was lower in patients receiving HD than in those with normal renal function [85]. Arterial and venous pharmacokinetic concentration data in that study indicated that sunitinib was not eliminated via HD. The study showed that a single dose of sunitinib was well tolerated in patients on HD without serious toxic effects.

There are no significant differences in the pharmacokinetics of sunitinib or its primary active metabolite (Su12662) between single and repeated administration or between healthy individuals and cancer patients. Previous studies have shown that plasma concentrations reach their maximum between 6 and 12 hours after a single oral dose of sunitinib, and bioavailability is unaffected by food [86]. The area under the plasma concentration-time curve (AUC) and maximum plasma concentration (C_{max}) increase dose-proportionately in the dosing. With repeated administration, steady-state concentrations of sunitinib and SU12662 are achieves in 10 to 14 days. Sunitinib accumulates 3 to 4 fold and SU12662 accumulates 7 to 10 fold.

Both sunitinib and SU12662 are metabolized primarily by cytochrome P4503A4 (CYP3A4), with SU12662 comprising 23% to 37% of the total drug exposure. Elimination is primarily via the fecal route with 61% of the administered dose; 16% of the administered dose is eliminated through the urine [87]. The terminal half-lives of sunitinib and SU12662 are approximately 40 to 60 hours and 80 to 110 hours, respectively.

Renal insufficiency is common in patients with solid tumors and occurs in more than 50% of all cases studied [88]. Because renal elimination plays a minor role in clearing sunitinib, renal impairment would not be expected to have a significant effect on its pharmacokinetics. A population pharmacokinetic analysis indicated a lack of effect of sunitinib or Su12662 pharmacokinetics in patients with mild to moderate renal impairment with calculated creatinine clearance (CL_{cr}) values in the range of 32 to 347 mL/min [28,29]. However, data were unavailable for patients with severe renal impairment (CL_{cr}<30 mL/min) or patients on hemodialysis.

Thus, based on the pharmacokinetic data, the currently approved starting dose of sunitinib 50mg on Schedule 4/2 is likely appropriate for patients with severe renal impairment. These findings may be relevant to clinical practice, especially for RCC patients who have undergone nephrectomy, for patient groups such as the elderly, or for those with comorbid conditions such as diabetes who often report coexisting renal insufficiency [88-90].

Comparing the outcome data of the patients on hemodialysis with the non-hemodialysis-dependent patients, partial responses were achieved in three patients undergoing hemodialysis and in three non-hemodialysis-dependent patients. Stable disease was observed

in an additional six patients undergoing hemodialysis compared with three non-hemodialysis-dependent patients, and one dialysis patient developed progressive disease in comparison with two non-hemodialysis patients.

The pharmacokinetic analyses of sunitinib and its main metabolite in patients on hemodialysis must be considered further [82,84]. Outcomes in some series of patients, in terms of median PFS and 12-month OS, were similar to those observed in patients with normal renal function treated with TKIs. Moreover, there were no significant differences in outcomes (PFS and OS) among patients who started TKIs on reduced doses and those who received full doses.

The sunitinib dose was 50 mg daily irrespective of hemodialysis in Park's report [77]. In contrast, Zastrow [68] started with a sunitinib dose of 25 mg daily, irrespective of hemodialysis, and increased to 37.5 mg and 50 mg according to the patients' tolerance. Overall responses were complete response (CR) by the patient in Park's report, and CR by one patient and stable disease by the other patient in Zastrow et al.'s report. However, the dose intensity in these two reports was similar to that used with non- ESRD patients and it seemed that higher cumulative doses of the sunitinib resulted in better responses.

Comorbid Associated Conditions

Diabetes mellitus

Diabetes mellitus (DM) is an extremely complex disorder involving insulin resistance and β-cell dysfunction. Insulin receptors and IG1 receptors activate a number of post-receptor cascades including Irs, Sgk or Akt-2 protein kinases inducing protein synthesis, antilipolysis and cell survival [91]. TKIs influence glucose metabolism, with both elevated and decreased blood glucose levels that have been attributed to TKI treatment. The molecular mechanism by which TKI controls glucose homeostasis remains unknown. More disturbing is the observation that the same TKI (for instance, imatinib or sunitinib) can be associated either with hyperglycemic or TKIs seem to have limited effect on lipids. Hyperglycemia has been reported with sunitinib in 15% of patients with metastatic RCC [1], while it was not reported in phases III trials of patients with advanced P-NETs or GIST. In contrast, some patients treated by imatinib or sunitinib also presented hypoglycemia and/or regression of long-standing diabetes [92-97].

Recent reports suggest that sunitinib may affect glucose metabolism in both diabetic and non-diabetic individuals [98,99]. Interestingly, sunitinib use has been associated with improvements of glycemic control in diabetic patients [96,97]. Moreover, sunitinib has resulted in reversal of type 1 diabetes in experimental animals [100] and there are two recent reports of patients with established type 1 diabetes who were able to discontinue insulin for several months, whilst being on sunitinib treatment for a PNET and for renal cell carcinoma, respectively [101,102]. In 2006 have been reported similar observations in mice models using AG-013736, which is also a tyrosine kinase inhibitor of VEGFR-1, -2 and -3. In this animal model, a 21-day pre-treatment with AG-013736 improved blood glucose handling [103]. According to the authors, this phenomenon could be partially related to significant quantitative and qualitative capillary regression in pancreatic islets. Interestingly, this VEGF-dependant phenomenon was reversible after cessation of the treatment. Second, IGF-1 regulates VEGF expression through HIF1-α [104].

The exact mechanism through which sunitinib lowers plasma glucose levels is currently unclear. Several potential explanations have been proposed, mainly based on the effects of imatinib, another TKI, on carbohydrate metabolism. Most likely via a protective, antiapoptotic effect on β-cells mediated by nuclear factor-κB; sunitinib have an impact on insulin resistance by interfering with the IGF-1 pathway [96]. The platelet- derived growth factor signaling pathway, through which sunitinib works, was recently shown to control age-dependent β-cell proliferation in mouse and human pancreatic islets [105]. The phosphorylation of these proteins is crucial in insulin signaling and in controlling the activity of cellular insulin effectors, such as enzymes. Inhibition of phosphorylation by imatinib may result in better signaling, better functioning of effectors, or both, with improvement in insulin sensitivity. TKIs may also inhibit phosphorylation processes involved in impaired insulin secretion. It is important to emphasize that inflammation and oxidant stress, which seem to play a crucial role in the pathogenesis of type 2 diabetes mellitus [106], share several mechanisms with aberrations in cell differentiation, growth, and proliferation.

There are reported an interesting clinical case of remission of type I diabetes after sunitinib treatment [102].

A decrease of glucose uptake in a context of concomitant gastrointestinal toxicity cannot be excluded, and oral glucose uptake could consequently be reduced. In addition, direct intestinal toxicity of sunitinib has been reported, and this could induce vitamin malabsorption [107]. However, the hypothesis of altered glucose transport is not confirmed, as glucose handling was not modified in the animal model after an intravenous compared with an oral glucose challenge after treatment [103]. Finally, drug-drug interaction (between sunitinib and blood glucose-lowering drugs) could be advanced as an additional basis for our findings. From a clinical perspective, it is important that glucose levels of patients treated with sunitinib are monitored on a regular basis.

Because treatment with TKI may be associated with hypo- or hyperglycemia, it is recommend measuring FPG and HbA1c before initiating the TKI treatment. FPG will be checked every two weeks during the first month then once every month. HbA1c will be measured every three months. In a patient with known diabetes, SMBG will be reinforced.

Renal insufficiency

Chronic kidney disease, defined as a glomerular filtration rate of <60 mL/min/1.73 m^2 [108], is commonly seen in patients with RCC, occurring in 37% in one case series [109]. In a retrospective cohort study of 10 886 patients with RCC, 16.4% and 21.8% of patients progressed to dialysis or renal transplantation after partial and radical nephrectomy, respectively [110]. In addition, RCC is a complication of chronic kidney disease [111]. Recently reported a correlation between the risk of cancer in men and chronic kidney disease, beginning when the estimated glomerular filtration rate (eGFR) falls below 55 mL/min/1.73 m^2. When the eGFR is <40 mL/min/1.73 m^2 the increased risk of cancer was found to be site-specific for bladder, renal and lung cancers. In addition [112] found that in the 5 years leading to renal replacement therapy, the observed number of cases of renal cancer was 193, compared with an expected 14 according to corresponding population cancer incidence rates.

The prevalence of RCC is higher among patients with end-stage renal disease and recipients of kidney transplants than in the general population, and these patients have distinct clinical and pathological RCC features [113-115]. The incidence of RCC is also higher in

patients with chronic kidney disease than in the general population, and a significant number of these patients show progression to end-stage renal disease, with or without nephrectomy [88,90,113].

The sunitinib-related adverse effects in patients with renal insufficiency were very similar to those in patients in previous phase III studies that excluded patients with renal insufficiency. In a meta-analysis, there are describe the elevation of serum creatinine of any grade in 65% of patients treated with sunitinib with a risk ratio of 13.5 [116]. Deterioration of renal function is a well-recognised adverse effect of treatment with sunitinib. In the study by Billemont et al. [96], renal toxicity occurred in 37.5% of patients, but this adverse event was associated with better overall survival and response rate.

The safety of sunitinib in a small population of patients with severe renal impairment or on haemodialysis, is supported by the observation that the overall incidence of dose modifications, discontinuations and AEs in this cohort is similar to that seen within the pivotal phase III trial and the expanded-access trial.

In a posterior study, in patients with mRCC with renal insufficiency treated with sunitinib, the median PFS was 12.2 months and the median OS was 26.3 months [117]. In the expanded-access trial assessing the safety of sunitinib in patients with mRCC, the median PFS was 10.9 months and the median OS was 18.4 months, which are considerably shorter than those seen in the current study [2].

Clearly showed that plasma exposure to sunitinib and SU12662 was significantly lower in patients requiring haemodialysis compared with those with normal renal function [84]. They attributed this to decreased drug absorption and consequently a lower bioavailability in patients with end-stage renal disease. A risk for under-dosage of sunitinib in those patients, even when administered at its usual dose, is therefore implicated.

Sunitinib and its active metabolite SU12662 are primarily excreted in the faces, but 15-20% is eliminated really [118]. The pharmacokinetics of sunitinib indicated that renal function would not be majorly affected.

Although, previous reports indicated that, following treatment with sunitinib patients with mRCC with renal insufficiency experienced deterioration of renal function [85], however, these patients did not display differences in the efficacy or toxicities of sunitinib. Several cases concerning dialysis-dependent mRCC patients treated with sunitinib have been reported [77,82,119].

No significant difference in the rates of severe toxicity were observed between the cohorts, with 4 (18.2%), 34 (14.5%) and 73 (13.7%) and patients with a toxicity event in the severe RI, moderate RI and mild RI/normal GFR groups, respectively. The retrospective analysis based on a large registry-based patient cohort indicates that sunitinib is effective in patients with reduced glomerular filtration, including patients with GFR below 30ml/min/1.73m^2 as well as GFR between 30 and 60ml/min/1.73m^2 [120].

Hepatic impairment

Sunitinib is metabolized mainly by cytochrome P4503A4 (CYP3A4) to form the active metabolite, SU12662; SU12662 is also metabolized by CYP3A4 6 [90]. SU12662 comprises 23-37% of the total exposure [121]. Sunitinib and SU12662 are the major drug-related compounds that have been identified in plasma, urine, and feces (representing 91.5, 86.4 and 73.8% of radioactivity in pooled samples, respectively); minor metabolites have been identified in urine and feces, but are generally not found in plasma. In a mass balance study, 61% of the administered sunitinib dose was eliminated in feces, with renal elimination accounting for 16% [87,122].

In a population pharmacokinetic analysis, no relationship was observed between liver enzyme levels (evaluated using baseline alanine aminotransferase [ALT] values [0-35 U/l, n=175; 36-69 U/l, n=23; 70-140 U/l, n=6; >140 U/l, n=1]) and sunitinib or SU12662 pharmacokinetics [86].

The pharmacokinetics of sunitinib, SU12662, and total drug were similar in subjects with mild or moderate hepatic impairment as compared to subjects with normal liver function so its apparent oral clearance was not significantly different in subjects with hepatic impairment compared to normal subjects. The percentages of unbound sunitinib and SU12662 were slightly smaller in the subjects with hepatic impairment compared with the normal group. Unbound sunitinib exposure ($AUC_{0-\infty,u}$, $AUC_{0-last,u}$, and $C_{max,u}$) was not significantly changed in subjects with mild and moderate hepatic impairment. The results demonstrated that mild or moderate hepatic impairment, defined using the CP classification, and did not significantly alter sunitinib systematic exposure ($AUC_{0-\infty}$, AUC_{0-last}, and C_{max}) after a single dose. The half-life of sunitinib while consistent with previous reports [86,87] was longer in both groups with hepatic impairment compared with the normal group (mild: 79.5h; moderate: 79.2h; normal: 63.8h).

It is possible that the longer half-life of sunitinib in subjects with hepatic impairment may be explained by a larger volume of distribution in these subjects, resulting from an increase in extracellular fluid (e.g., ascites, peripheral edema), as has been reported [121,123-125]. Protein binding of sunitinib was similar between groups, although slightly less in the normal group compared with the groups with hepatic impairment. Significant differences between the groups could not be concluded as the variability in the protein-binding assay could not be quantified.

Sunitinib is metabolized mainly by cytochrome P4503A4 (CYP3A4). However, in population pharmacokinetic analysis, it has been observed that the pharmacokinetics of sunitinib and its metabolite were similar in subjects with mild or moderate hepatic impairment as compared to subjects with normal liver function so its apparent oral clearance was not significantly different in subjects with hepatic impairment compared to normal subjects, although it was noted a longer half-life of the drug in subjects with hepatic impairment, probably by a larger volume of distribution.

Integrating Surgery

Surgical intervention is the primary treatment for early- stage RCC; however, surgery alone has limited benefit in patients with metastatic disease, except for palliative reasons [109]. For advanced or metastatic disease, nephrectomy may only be curative if all metastatic deposits are excised [125]. Therefore, a combination of surgery and targeted therapy is increasingly being used for locally advanced and mRCC in an attempt to improve patient outcomes.

The role of surgical intervention in patients with metastatic renal cancer is twofold: to render a patient clinically free of all sites of primary disease and metastases, termed nephrectomy / metastasectomy, or to resects the primary tumor in the face of unresectable metastatic disease prior to the initiation of systemic therapy, termed cytoreductive nephrectomy [113].

In advanced RCC, surgery has undergone a transformation over the past several decades. Historical indications for nephrectomy have included palliation of pain, intractable hematuria, and paraneoplastic symptoms [126]. However, angioinfarction may serve as a less invasive alternative to palliative nephrectomy at present.

Debulking nephrectomy has become the standard of care in appropriately selected patients with mRCC, based on an overall survival advantage reported in two randomized prospective phase III trials [127,128] and a combined meta-analysis [129]. Several other retrospective series have shown a relationship between the percentages of tumour removed and improved outcome [130]. Initially proposed removing the primary tumour if its bulk was greater than that of the metastasis. Later [131], it was identified that patients with >75% of the tumour removed at the time of nephrectomy as most likely to benefit from subsequent interleukin-2 immunotherapy. Most recently [132], showed that >90% of the tumour burden removed at nephrectomy was associated with longer overall survival. However, this last study included a large percentage of patients who also underwent distant metastasectomy.

In patients undergoing radical nephrectomy for RCC at the Mayo Clinic who had either distant metastases at the time of diagnosis or subsequently developed metastases, many factors as constitutional symptoms at nephrectomy, metastases to the bone or liver, metastases in multiple simultaneous sites, metastases at nephrectomy or within 2 years after nephrectomy, tumor thrombus, nuclear grade 4, and coagulative tumor necrosis were predictors of poor survival. In contrast, complete resection of all metastatic sites was associated with improved survival. These authors recommend an aggressive surgical approach to metastatic RCC, including debulking nephrectomy and metastasectomy, when feasible [133].

It has been demonstrated in other series that lymph node status is associated with poor outcome after cytoreductive nephrectomy and immunotherapy [134,135].

The spontaneous regression of metastatic disease occurs almost exclusively in the lung and only after removal of the primary tumour, many authors have speculated that the primary tumor possesses immunosuppressive properties [136]. One potential mechanism is that the tumor acts as an immunological 'sink,' drawing and trapping antibodies and circulating immune cells so that they cannot exert an effect on metastatic sites [130,136,137]. Tumor cells may also impair the activity of circulating immune cells by causing dysfunction of T-cell receptors [138] and by interfering with signal transduction mechanisms, [139-141] antigen processing, [142] and expression of major histocompatibility complex antigens [143]. There is also evidence that RCC may induce apoptosis of tumor-infiltrating lymphocytes [144,145]. In addition, renal cancer cells have been shown to produce inhibitory cytokines that may actively suppress immunological responses [146,147]. In this section we review the main studies that integrate anti target therapies to surgery.

Cytoreductive nephrectomy

There are several theoretical advantages to cytoreductive nephrectomy (CN) prior to the initiation of systemic therapy. Several authors cite the palliation of symptoms related to the primary tumor such as pain, hematuria, and paraneoplastic syndromes. Also, some patients may experience an improvement in its performance status (PS) following debulking nephrectomy. There are published data among 32 patients treated at Indiana University, 72% had a PS equal to or better than their pre-operative status, including four patients with a PS of 2 who improved to 0 or 1 postoperatively [148]. Another potential advantage of CN is the concept of debulking: by removing the primary tumor, fewer cancer cells are available to contribute to the metastatic process.

Another theory regarding the effect of CN is related to the angiogenic properties of the tumor [149]. Increased levels of serum VEGF [150-152] as well as multiple other angiogenic growth factors have been demonstrated in patients with RCC [153,154]. Removal of the primary tumor along with reduction of circulating angiogenic factors would thus allow stabilization of metastatic growth rates and potentially enhanced immune defenses against metastatic sites.

The adoption of CN as a valid step in the treatment of metastatic RCC comes from 2 randomized phase III trials and their combined meta-analysis, evaluating the role of cytoreductive nephrectomy in the immunotherapy era. Both studies used the same study design, patient eligibility criteria, and treatments. In both trials a significant improvement in overall survival (OS) was seen in patients randomized to nephrectomy prior to IFN-a therapy [127-129].

Although CN was largely accepted as a necessary step in the treatment of mRCC, this concept is now challenged with the use of targeted therapy. Many believe we should abandon cytoreductive nephrectomy and adopt a pure systemic treatment approach.

To present, there are no data to directly show the benefit of CN in the targeted therapy era. In a published MD Anderson experience [155], results obtained from 188 consecutive patients who received targeted therapy and never underwent cytoreductive nephrectomy were reported. The median survival for this group was 10.4 months, very different from that observed in the phase III trials of sunitinib, bevacizumab, or pazopanib, which range from 22 to 26 months.

Other trial [156] included 314 patients treated with targeted therapy, and compared 201 patients who underwent cytoreductive nephrectomy with 113 patients who did not. In the multivariable analysis, CN was associated with improved overall survival in the general cohort (19.8 months in patients who underwent nephrectomy vs. 9.4 months in those who did not, hazard ratio 0.68), but on sub analysis it was noted that patients with poor risk features derived marginal benefit from surgery.

Two prospective, single arm phase II studies, investigating 2 cycles or 3 cycles of sunitinib prior to nephrectomy in mCRC were evaluated centrally with the objective of evaluate prospectively the safety and efficacy of upfront sunitinib in this patients. With the exception of the number of cycles of sunitinib given, both studies had identical design and entry criteria. Authors reported that no patients became inoperable due to local progression of disease, but 20% developed progression of systemic disease prior to surgery. Nephrectomy was possible in 71% of patients, the median progression free survival was 9 months (95% CI: 5-15 months) and no significant differences was observed between of 2 vs. 3 cycles of sunitinib prior to nephrectomy [157].

Actually, two ongoing trials are being conducted to address the question about the role of the TKI in the CN. Both studies were designed as prospective trials using sunitinib. The French trial CARMENA (NCT00930033) is a randomized, non inferiority, phase III trial evaluating the importance of nephrectomy in patients presenting with mRCC treated with sunitinib and aims to enroll

576 patients. It was designed to compare OS (primary endpoint) in patients treated with sunitinib alone versus treated with CN followed by sunitinib. The other trial was designed by EORTC (NCT01099423) to investigate the optimal timing of CN, comparing PFS in patients treated with cytoreductive nephrectomy followed by sunitinib versus sunitinib followed by surgery. The primary outcome will be the PFS. We must await the results of these studies to determine if the role of cytoreductive nephrectomy with sunitinib is similar (or not) to that it has with cytokines.

Neoadjuvant therapy

There is a rationale for presurgical targeted therapy and investigation of pretreated primary tumor tissue [158]. Neoadjuvant therapy (NT) should refer to the administration of targeted therapy in RCC to improve surgical resection of otherwise resectable/no metastatic disease. Several potential clinical benefits of a neoadjuvant or presurgical approach with targeted therapy can be envisaged that may translate into a prolongation of PFS or OS.

NT may result in down staging of the primary tumor, which may, in turn, facilitate surgical resection [159]. In particular, patients with technically unresectable primary tumors, bulky regional lymph node metastases, or caval thrombi, in whom complete resection may be achieved after pretreatment, may potentially benefit most from this approach. Some authors have included patients with a large distant metastatic disease burden in the definition of unresectable disease [160].

Initial reports suggested that TKIs, can induce some downsizing at the level of the primary tumor. In patients treated with sunitinib for advanced RCC who had not had prior nephrectomy, one study showed tumor volume reduction of 31%, which was associated with an increase in the volume of necrosis (39%) [161]. There is additional evidence from several case reports where TKIs were used to downsize caval thrombi and retroperitoneal lymph node metastasis followed by a successful resection of the *lesions* [162-164]. However, unlike downsizing, down staging or complete histologic remission are rare events and only a few cases have been described [165].

Several presurgical phase 2 trials and retrospective series had showed that the median downsizing of the longest diameter of the primary tumor with various targeted agents ranged between 6% and 14.5%, while Response Evaluation Criteria In Solid Tumors (RECIST) partial response of the primary tumor ranged between 3.3-6%.

There are small and retrospective series showing that preoperative targeted therapy can be administered without an increased risk of morbidity. The limited experience to date suggests that the shorter half-lives of sunitinib allow discontinuation of this agent just a few days prior to surgery [166].

One trial [167] assessed the activity of neoadjuvant sunitinib on primary renal tumors in patients with advanced renal cell carcinoma as well as the feasibility and safety of subsequent surgical resection. A total of 19 patients with advanced RCC deemed unsuitable for initial nephrectomy due to locally advanced disease or extensive metastatic burden were treated with 50 mg sunitinib daily for 4 weeks on followed by 2 weeks off. Tumor response was assessed by Response Evaluation Criteria in Solid Tumors every 2 cycles and the rate of conversion to resectable status was estimated. Partial responses of the primary tumor were noted in 16%, 37% had stable disease and 47% had disease progression in the primary tumor. Overall tumor response included 2 patients with partial response, 7 with stable disease and 10 with disease progression. At a median follow-up of 6 months, 4 patients (21%) had undergone nephrectomy and 5 died of disease progression. No unexpected surgical morbidity was encountered. Viable tumor was present in all 4 specimens. Sunitinib was associated with grade 3–4 toxicity in 7 patients (37%) and treatment was discontinued in 1 due to toxicity.

These studies allow us to conclude that administration of sunitinib in patients with advanced renal cell carcinoma, with the primary tumor in place, is feasible, safe and can lead to a reduction of tumor burden, although the absence of results from prospective studies with good design does not allow us to make recommendations at this time.

Postsurgical therapy

Patients without metastases usually are treated with a radical surgical approach. Also, some patients with metastatic disease are treated with surgery of their primary tumor and additional metastasectomy. Although the absolute curative impact of metastasectomy remains uncertain, operative intervention can also provide effective palliation for symptomatic metastatic disease to sites such as bone, brain, and adrenal gland [168]. In both scenarios, a percentage of patients will have recurrence and eventually die because of the disease. Therefore, appropriate adjuvant treatment for reduction of relapse risk, could be very useful in patients at a higher risk of relapse. At present, several therapies (immune, hormonal and targeted therapies) has been proven, but no one has show be useful in this setting [169].

A meta-analysis of adjuvant therapies (chemotherapy, immune therapies, and hormonal treatments) for locally advanced RCC was published in 2011 [170] and it concluded that, because there was no evidence of any benefit and it caused substantial toxicity, there was no support for using systemic therapy in the adjuvant setting, In this analysis, no targeted therapy were included because no trial with this treatment was completed at that time.

Targeted therapies are subject of current research in this subset of patients, but so far have shown some benefit. We have recently known the initial results from ASSURE (E2805), a phase III trial comparing sunitinib and sorafenib in adjuvant setting in patients with resected primary disease at high risk. These preliminary results indicate that it is a negative study as their primary objective, DFS, is not met: median time to disease recurrence did not differ between those who received sorafenib or sunitinib after surgery (median 5.8 years) and those treated with placebo (median 6 years) [171].

Several other trials are ongoing, testing the role of targeted therapy in this scenario. One of this trials is the Sunitinib Treatment of Renal Adjuvant Cancer Trial (NCT00375674), a phase III randomized, double-blind, placebo-controlled trial, with 500 patients included fulfilling high-risk criteria (UISS) and testing sunitinib for 1 year as adjuvant therapy. Results about it primary end point, disease-free survival, are expected through 2017.

The encouraging response data, both in primary tumors as in metastases, suggest a probable role of targeted therapies integrating with surgery as a rational step in the evolution of RCC treatment. Presently, we do not have definitive evidence supporting changes in the current treatment paradigms. In the absence of prospective randomized data, CN remains a part of the treatment algorithm for patients with metastatic disease and good PS with a resectable tumor. By contrast, patients with poor overall health, large tumor burden beyond the kidney, or highly aggressive disease are unlikely

to benefit from nephrectomy, and should receive systemic therapy first. The hypothesis of the published analysis was that in the era of VEGF-targeted therapy, a greater percentage of tumour volume removed with debulking nephrectomy would be associated with an improved PFS. The neoadjuvant use of sunitinib administration in patients with advanced renal cell carcinoma appears to be feasible, safe and can lead to a reduction of tumor burden. We must await the final conclusions of ongoing studies evaluating the role of sunitinib in patients at high risk of recurrence after surgery as primary therapy for their malignancy.

Individualized Sunitinib Therapy

The data in the literature seem to give a prominent role to sunitinib malate, a specific inhibitor of the tyrosine- kinase receptors, VEGFR and PDGFR, as first-line treatment of mRCC. At the same time, as one of the most significant aspects of targeted molecular therapies is the need to continue the treatment until progression of the disease, special attention must be addressed to monitoring any drug-related side-effects, while at the same time under- standing the mechanisms that give rise to them and their control in order to maintain adequate dose intensity of the drug given.

Animal studies have revealed that total drug plasma concentration (Sunitinib plus its active metabolite) in the range of 50–100ng/mL was capable of inhibiting VEGFR-2 and PDGFR-α phosphorylation. Toxicological evaluation of animal models revealed bone marrow depletion and toxic effects in rats and monkeys, as well as adrenal micro hemorrhages in rats. To minimize potential bone marrow and adrenal toxicities in clinical evaluation, health authorities requested an intermittent dosing schedule. Sunitinib was thus studied in cancer patients using various schedules, including a 3-week cycle comprised of treatment for 2 weeks followed by a 1-week rest period (schedule 2/1), a 4-week cycle comprising treatment for 2 weeks followed by a 2-week rest period (schedule 2/2), or a 6-week cycle comprised of a 4-week treatment followed by a 2-week rest period (schedule 4/2).

The longer-term impact of Sunitinib-associated toxicities is also recognized to be increasingly important as patients are living longer [172]. The high incidence of dose reduction, treatment-discontinuation and AEs associated to sunitinib treatment lead scientist to investigate alternative schedules of sunitinib in phase I-II trials and retrospective analyses, aimed at optimizing the sunitinib dosing schedule. In addition, pharmacokinetic analysis of data from studies in healthy volunteers and patients with cancer demonstrated high inter-patient variability in pharmacokinetics with a coefficient of variation in the range of 40-60%. These observations support a reversal of the desired pharmacodynamic effect during the 2 weeks in which patients were off the drug and highlight the importance of maintaining sunitinib drug levels, but do not address which dose/schedule achieves this more optimally in patients with RCC.

The most common toxic reactions requiring dose reduction or treatment interruption were grade 3 hand-foot syndromes (HFS), grade 3 diarrhea, grade 3 thrombocytopenia and grade 3 neutropenia. The most commonly used sunitinib treatment schedule is 50 mg daily for 4 weeks followed by a 2-week interval off treatment (schedule 4/2). Although previous reports have suggested that a maximal dose and area under the serum concentration-time curve (AUC) may intensify the therapeutic response [173], a phase III clinical trial showed that more than 50% of patients required modification of the sunitinib dosage or interruption of treatment owing to drug toxicity [1]. The larger the dosage, the better the effect, but also the greater the toxicity.

Inability to deliver adequate sunitinib dose is relevant. In real world clinical practice, maintenance of the dose intensity of sunitinib is frequently challenging as a result of treatment-related adverse events (AEs), such as fatigue, hypertension, HFS and thrombocytopenia, resulting in the necessity of dose reduction or interruption in a large proportion of patients receiving Sunitinib [174], whereas analyzed pharmacologic data from six clinical trials, and reported that patients with high-level drug exposure (AUC) showed longer overall survival, prolonged time to progression and increased reduction of the tumor burden [175]. Minimizing the time without therapy may be important as tumor progression occurs during treatment interruption [38,176].

Thus, the substantial proportion of patients who may require dose reduction/interruption with sunitinib could lead to lower plasma levels and reduced clinical benefit. Alternative schedules of sunitinib have been explored with the goal of improving drug tolerance and maintaining dose intensity.

Classic-traditional schedule

The standard dosing schedule of sunitinib (schedule 4/2) was based on preclinical data that the target plasma level of 50 ng/mL of sunitinib and its primary metabolite, (SU12662), was maintained for at least half of the daily dosing interval at this dose and schedule [118]. Preclinical pharmacokinetic and pharmacodynamic data showed that target plasma concentrations of Sunitinib and their metabolite in the range of 50–100 ng/mL were capable of inhibiting phosphorylation of PDGFR-b and VEGFR-2, suggesting that this was the clinically significant range. While initial studies planned to provide continuous administration, schedule 4/2 was used to allow patients to recover from potential bone marrow and adrenal micro hemorrhage observed in animal models [118]. Dose-limiting toxicities (DLTs) included fatigue, hypertension, and bullous skin toxicity [118].

Based on these findings, several subsequent clinical trials examined schedule 4/2, and this regimen was approved due to its excellent antitumor activity and manageable safety profile [1,177].

Continuous daily dose

One trial investigated the safety, tolerability and pharmacokinetics of Sunitinib 50 mg 2/1 schedule [178]. Twelve patients with advanced refractory malignancies were treated with sunitinib in this way. Pharmacokinetic studies revealed no significant accumulation of Sunitinib or SU12662. This schedule was tolerable, and no significant drug accumulation was demonstrated, being the safety profile consistent with the standard one.

In a phase II randomized study, EFFECT study [173], the Sunitinib standard schedule was compared with a continuous daily dose schedule (CDD) of 37.5 mg in a total of 146 naive patients with clear cell mRCC. Median time to tumor progression, the primary end point, was 9.9 months for 4/2 schedule and 7.1 months for the CDD schedule (HR 0.77; 95% CI, 0.57 to 1.04; p=0.090) with no difference observed in overall survival (23.1 vs. 23.5 months; p=0.615), commonly reported adverse events, or patient-reported kidney cancer symptoms. Schedule 4/2 was statistically superior to CDD in time to deterioration, progression and disease related symptoms (p=0.34). The rate of patients who discontinuities sunitinib because of adverse events was 11% for 4/2 schedule vs. 15 % for CDD, drug interruptions were 65% (4/2) vs. 62 % (CDD) and dose reductions (4/2 vs. CDD; 36% vs. 43%). The authors concluded that no benefit in efficacy or safety for CDD was demonstrated.

Three other non-randomized phase II studies on continuous sunitinib dosing have been published, including more than three hundred patients in total [179-181]. The ORR varied from 20 to 35%, median PFS from 8.2 to 13 months and median OS from 19.8 to 25 months, all comparable to the study of Motzer et al. [2] 2012 and also to the pivotal phase 3 trial. Phase II studies with CDD [180-182] had percentage of dose reductions and treatment discontinuations due to AEs which were comparable to the Motzer study [179].

Alternative schedule: biweekly schedule

The initial clinical trials with sunitinib employed intermittent dosing schedules with a 2-week off-drug period. This early schedule was selected based on the preclinical toxicology data available at the time clinical investigation was initiated. However, preclinical experiments have demonstrated tumor growth during the off-dosing period [183], suggesting that sunitinib may be most effective with more continuous dosing. These findings suggest that schedule 2/1 could be the optimal dosing schedule of sunitinib against mRCC that balances efficacy and toxicity, since treatment on schedule 2/1 resulted in a markedly improved QOL compared with that on schedule 4/2 by relieving the profile of sunitinib related AEs.

Rainbow study [184] is a retrospective, multicentre study that included 276 patients. 3 different treatment arms were: A (208 patients), who initiated at standard dose and continue to 2/1 schedule due to toxicity; group B (41 patients), with initial treatment 2/1 because of poor performance status and group C, 27 patients, who were treated on 4/2 (Control arm). A total of 211 consecutive patients treated with the 4/2 schedule in another institution served as external controls. Safety was the primary endpoint. Treatment duration (TD), progression-free-survival (PFS) and overall survival were also analyzed. There were clinical and histologic differences between treatment arms, as median age (62 and 61 years), percentage of clear cell carcinomas (94% and 87%) and good risk prognostic factors, 47% and 36% in group A and B. In group C median age was 59, 96 % had clear cell carcinoma and 22% were in good prognostic factor group. Median treatment duration was 28.2 months in the 4/2-2/1 group (total time spend with both schedules), 7.8 months in the 2/1 group and 9.7 months in external controls. Median PFS were 30.2, 10.4 and 9.7 months with median OS not reached, 23.2 and 27.8 months respectively.

Individualized treatment strategies to maximize dose and minimize time without therapy are important. A single-center retrospective review (Bjarnason G, 2014) was conducted on patients with metastatic renal cell cancer. Dose/schedule modifications (DSM) were done to keep toxicity (hematological, fatigue, skin and gastrointestinal) at grade ≤2. DSM was 50 mg 14 days on/7 days off with individualized increases in days of treatment. DSM-2 was 50 mg, 7 days on/7 days off with individualized increase in days on treatment. DSM-3 was 37.5 mg with individualized 7-days break. DSM-4 was 25 mg with individualized 7 day breaks. Multivariable analysis was performed for outcome as a function of patient and treatment variables. A total of 172 patients were included in the analysis, most of them had clear cell histology (79.1%) with sunitinib given in the first line therapy in 59%.The DSM-1 and 2 and DSM-3 and 4 groups had a progression-free survival (PFS) (10.9-11.9) and overall survival (OS) (23.4-24.5) that were significantly better than the PFS (5.3 months; p<0.001) and OS (14.4 months; p=0.03 and 0.003) for the standard schedule (50 mg, 28/14).

The study in Japanese population shows the comparable therapeutic efficacy of sunitinib delivered of the 2/1 schedule compared to 4/2 in the treatment of patients with mRCC [184]. The incidence of all AEs did not differ between the two dosing schedules, but HFS and diarrhea occurred at significantly lower incidence with Schedule 2/1. Dose interruptions were more likely in Schedule 4/2 than in the Schedule 2/1 group. In terms of efficacy, the objective response rate tended to be higher in 4/2 schedule than in 2/1 (50% vs. 32%), and median progression-free survival was longer in patients on 2/1 compared to 4/2 schedule (18.4 versus 9.1 months). These differences, did not reach statistical difference (p=0.14; p=0.13).

Najjar and colleagues [185] published a single center, retrospective experience, in 30 patients who changed from 4/2 to 2/1 after toxicity. 97% of patients on 4/2 had grade 3 or 4 toxicities that led to schedule 2/1. No grade 4 toxicities were reported and 27% had grade 3 (p=0.0001) on 2/1 schedule, being fatigue and hand-foot syndrome more significantly less frequent on 2/1 than 4/2 (p=0.0003; p=0.0004, respectively).

Some studies [186,187] have reported better quality of life with 2/1 compared to 4/2 regimen. The Restore study is the only that compares directly standard versus alternative 2/1 regimen [188]. 76 Asiatic patients were enrolled (38 to 4/2 schedule and 38 to alternative schedule). The primary endpoint was failure-free survival (FFS) at 6 months. 18 patients (ORR, 47%) in the schedule 2/1 achieved a partial response (PR) while one patient had a complete response and 11 patients had a PR (ORR 36%, 95% CI) in the schedule 4/2. With a median follow-up duration of 47 months, the medium time-to. Progression was 15.1 months in the schedule 2/1 and 10.1 months in the schedule 4/2 (HR 0.69, 95% CI, 0.39-1.20). FFS at 6 months was 44% in schedule 4/2 and 63 % in schedule 2/1. Patients in 2/1 were treated for a median of 7.7 months (95%, 3-12.3) of initial assigned schedule while patients with 4/2 were treated for a median of 5.7 months (95% CI, 5-6.5) (HR 0.54, 95% CI, 0.32-0.91, p=0.021). 7 patients in the 4/2 crossed over to the 2/1 schedule, while none in the 2/1 crossover to 4/2 regimen (p=0.004).

Neutropenia (all grade 61% vs. 37%; grade 3-4, 28% vs. 11%; p=0.0368) and fatigue (all grade 83% vs. 58%, p=0.0167) were most frequently observed with 4/2. There is a strong tendency of lower incidence of mucositis (all grade, 86% vs. 71%; p=0.116), and hand foot syndrome (grade 3-4 33% vs. 18%; p=0.143) and rash (all grade, 56% vs. 34 %; p=0.0648) with schedule 2/1. Much less patients in the 2/1 schedule required dose reduction; 32 % and 68% of patients had at least one dose reduction (p=0.021), in the 2/1 and 4/2 schedule arms respectively.

Sunitinib-free interval regimen

There are different smaller studies that support sunitinib free interval strategies. A small retrospective study reported the effects of stopping sunitinib therapy in patients who had experienced a complete response, with or without surgical metastectomy following response to sunitinib [182]. At median follow up of 8.5 months, disease had recurred in 5 patients, but in all cases re-introduction of sunitinib was effective in regaining disease control.

At the ASCO Annual Meeting 2013, has been presented their preliminary results on a prospective phase II trial of intermittent sunitinib in previously untreated patients with mRCC [189]. Toxicity was completely resolved during treatment stops, suggesting that this intermittent dosing sunitinib may be better tolerated without compromising sunitinib efficacy.

A randomized, multi-stage phase II/III study of sunitinib was published comparing temporary cessation with allowing continuation, at the time of maximal response, in the first-line treatment of locally advanced/mRCC (the STAR trial) [190].

Other schedules

In a retrospective analysis, patients who had at least a grade 2 toxicity during sunitinib therapy were switched to a modified schedule maintaining the same dose-intensity of 4/2 regimen: starting on Monday, 1 tablet/day for 5 consecutive days a week (days 6 and 7 off therapy) for 5 weeks and 1 tablet/day on days 1, 3 and 5 in the sixth week (days 2, 4, 6 and 7 off therapy) until disease progression [191].

The choice of an ideal schedule for single individual patient seems still so far, due to the lack of biological insights that may guide the decision-making process. Data on the efficacy and tolerability of sunitinib continuously daily dose schedule seems to be less effective and similarly tolerated than 4/2 standard schedule, and should not be suggested for mRCC patients. Although supported by retrospective and single studies, the 2/1 regimen seems to be effective and show better toxicity profile, compliance to treatment, and dose intensity compared to standard régimen and showed a lower incidence of dose interruption and a similar oncological outcome compared with the standard dosing schedule of 4-weeks-on and 2-weeks-off. The decision to switch to schedule 2/1 versus attempting dose reduction should be made at the discretion of the treating physician on the basis of the patient's subjective and objective toxicity, considering the timing and type of toxicity for each patient.

Conclusions

In the last decade, we have witnessed a change in the therapeutic management of patients with advanced RCC. The pivotal and expanded access, with TKIs and inhibitors of the mTOR pathway, studies has shown the ability to change the prognosis for these patients. Unfortunately, these studies are not always the reality of the practice of medical oncology at the inquiry reflected everyday and see how many subgroups of patients are not represented appropriately. Sunitinib was the first of these agents to be approved by the health authorities by making it the most experienced agent use, with publications and collection of experiences that allow some recommendations in the subsets of patients none included in the phase III studies.

In our real life practice, there are patients in special situations like elderly patients, bone metastases, hepatic impairment, type 1 and 2 diabetes, renal insufficiency and end-stage renal disease, haemodialysis, brain metastases, and unresectable surgery. Little is known about the activity of targeted therapies, such of sunitinib, in these subsets of patients. It could be a benefit of sunitinib treatment for these patients, with good tolerance, by personalizing treatment in each situation, even if that means changing the treatment schedule without losing effectiveness [1-191].

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