Can individualized sunitinib dose and schedule changes optimize outcomes for kidney cancer patients?

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Abstract

The recommended starting dose and schedule for sunitinib is 50 mg daily for 28 days, followed by a 14-day break with significant dose reductions to 37.5 mg (75% of starting dose), and then 25 mg (50% of starting dose) on the same schedule (four/two schedule). There are several reasons why these dose and scheduling recommendations may not be optimal for most patients, as outlined below.

Maximizing drug exposure is important

Increased steady state area under the curve (AUC) is associated with a longer progression free survival (PFS), overall survival (OS), and a higher response rate.[1] However, in 146 patients receiving the standard schedule of sunitinib,[2] there was no correlation between sunitinib "steady state trough concentrations values" on Day 29 (Cycle 1) and the need to dose-reduce based on toxicity, suggesting that pharmacokinetic (PK)-guided dosing alone would not be helpful to individualize dosing.[3] Furthermore, PK parameters can decline over time in spite of constant dosing, as has been described for both sorafenib[4,5] and pazopanib.[6] This may explain the clinical observation of reduced toxicity as patients stay on tyrosine kinase inhibitor (TKI) therapy. These observations led to our early attempts to individualize dose and schedule to toxicity,[7,8] assuming toxicity might correlate better with sunitinib pharmacodynamics (PD)[9] and would take into account the inter-individual differences in sunitinib PK, potential decline in PK over time, individual single-nucleotide polymorphisms, and interactions with other drugs and that can impact the PK for sunitinib.[10,11]

The maximum benefit from therapy may be achieved before Day 28 and a shorter break off therapy may limit rebound cancer growth

PK data from several sunitinib trials have shown that blood levels for sunitinib reach a steady state after 10–14 days (Data on file, Pfizer). These PK data are in agreement with our micro-bubble ultrasound data for 14 patients responding to sunitinib.[8] In eight patients, studied at baseline and after seven days and 14 days on therapy, tumour blood volume (a measure of antiangiogenic activity) decreased on Day 7 and again on Day 14. In six patients studied at baseline, and after 14 days and 28 days on therapy, blood volume decreased on Day 14 vs. baseline, but was stable or increased on Day 28 vs. Day 14 in four patients. Most patients showed a rebound in blood volume after a 14-day treatment break. These data show that most of the benefit from sunitinib may be achieved well before Day 28 and that the treatment break should be shorter than 14 days to avoid the tumour progression that can occur during treatment interruption.[12-14]

Minimum toxicity in patients on the 50 mg four/two schedule predicts for inferior response, PFS, and OS

We were the first to report significantly inferior response, PFS, and OS in renal cell carcinoma (RCC) patients experiencing minimal toxicity from sunitinib on the standard 50 mg four/two schedule compared to patients that developed toxicity and underwent the individualized dose/schedule changes developed in our centre.[8,15] The outcomes for 172 patients (79% clear-cell histology; sunitinib given as first-line therapy in 59%) were analyzed retrospectively. The two individualized dose/schedule groups (receiving 50 vs. 37.5 and 25 mg dose) had a PFS (10.9–11.9 months) and OS (23.4–24.5 months) that was 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 four/two schedule in patients with minimal toxicity.

Subsequently, other retrospective studies[16,17] have confirmed our observation of an inferior outcome in sunitinib-treated RCC patients with minimal toxicity on the 50 mg four/two schedule. Most notably, a retrospective analysis[3] of the phase 3 trial comparing sunitinib to interferon (A618103, 375 patients)[18] and the phase 2 EFFECT trial (146 patients)[2] showed an inferior partial response rate and PFS in patients who continued on the standard schedule with minimum toxicity (25.4% and 8.1 months in A618103, 22.1% and 5.8 months in EFFECT) vs. those who required dose changes due to toxicity (60% and 14 months in A618103, 51% and 13.4 months in EFFECT).

The ongoing prospective study of individualized sunitinib

The data described above were the basis for the ongoing prospective phase 2 trial of individualized sunitinib given first-line to previously untreated patients with clear-cell RCC. It was hypothesized that the poor outcome in patients who remain on the full-dose, standard four/two schedule without toxicity was due to underdosing and that toxicity-driven dose/schedule changes would optimize drug exposure for each patient. Mature data from this trial will be submitted in 2017, but preliminary data were presented at ASCO 2015.[19]

Fig. 1 shows how dose and schedule are individualized on this trial. Table 1 shows the dose/schedule distribution for 102 eligible patients. Twenty patients (19.6%) were dose-escalated to a 62.5 or 75 mg dose. This is the group of patients who would be expected to do poorly if they remained on a 50 mg dose on the four/two schedule with no toxicity. Another 45% of patients continued on the 50 mg dose, but for less than 28 days, thus avoiding dose reduction to 37.5 mg. Only 20% and 7% of patients were dose-reduced to 37.5 mg and 25 mg, respectively, a much lower percentage than in other trials, and only 6% of patients came off therapy due to toxicity (15–20% in other trials). More than 65% of patients received improved dose intensity as compared to standard dosing criteria.

Table 2 shows the response rate compared to the comparator trial (EFFECT), which had identical eligibility criteria as this trial, and the COMPARZ trial comparing sunitinib and pazopanib first-line. The three trials in this table had near identical distribution of patients to the good (30%), intermediate (60%), and poor (10%) Memorial Sloan-Kettering Cancer Center (MSKCC) risk groups and the same 80% nephrectomy rate. The response rate on the individualized dosing trial compares favourably to the other studies in this table, with a 48% response rate and 89% clinical benefit rate (complete response + partial response + stable disease). It is notable that only 10.8% of patients were refractory to sunitinib in this study, lower than in the other studies with sunitinib to date. When these data were reported, 43% of patients were still on sunitinib therapy and, therefore, it was too premature to report on PFS or OS.

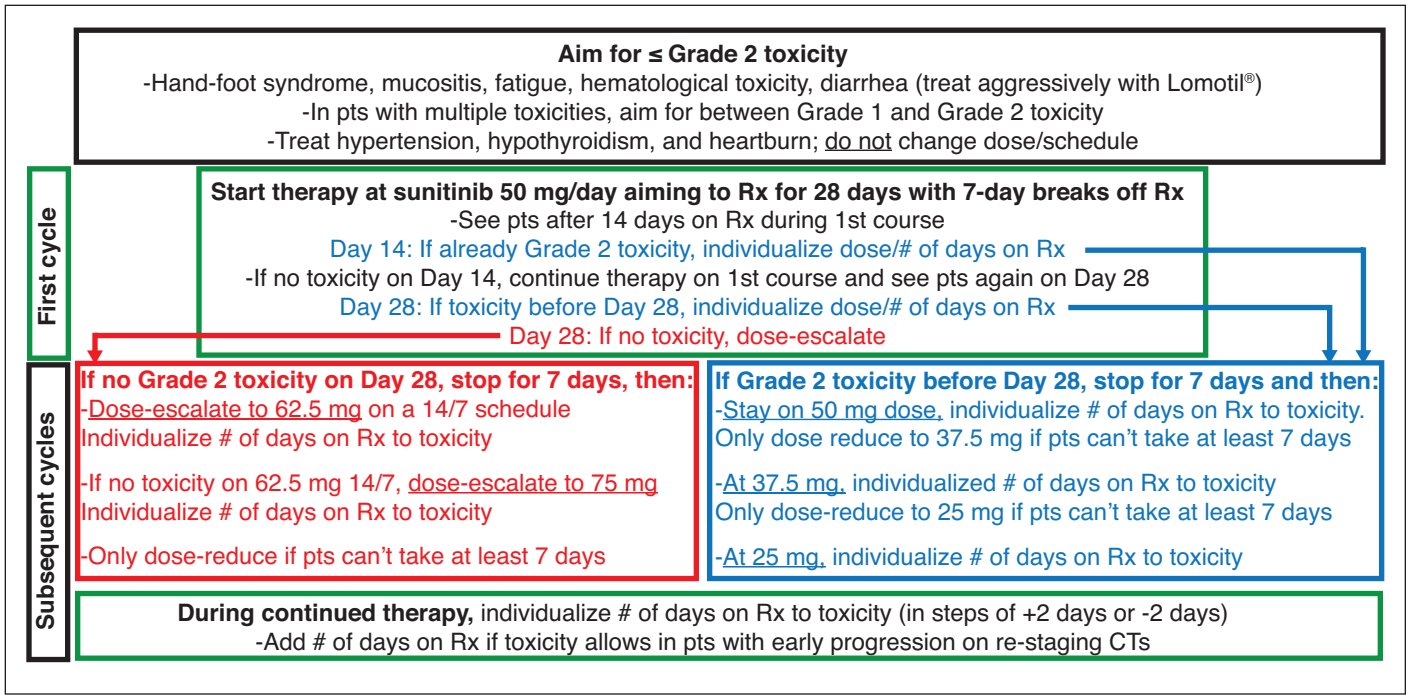

Fig. 1. Algorithm for individualized sunitinib dose/schedule based on toxicity.[19] CT: computed tomography; pts: patients; Rx: treatment.

Table 1. Dose schedule distribution for 102 patients[19]

Sunitinib dose (mg)	Schedule (days on/off)	No. of patients currently on treatment or who came off treatment on this dose and schedule	More than 65% of patients with improved dose intensity vs. standard dose criteria
75	16/7	1	20 patients (19.6%) dose-escalated
75	14/7	4	
75	10/7	1	
75	7/7	2	
62.5	16/7	1	
62.5	14/7	5	
62.5	12/7	1	
62.5	7/7	5	
50	28/7	7	8 patients (7.8%) on a 28-day schedule
50	28/14	1	
50	24/7	2	In 46 patients (45.1%), 50 mg dose was maintained with fewer days on treatment
50	21/7	1	
50	16/7	3	
50	14/7	20	
50	11/7	1	Would have been dose-reduced by standard criteria
50	9/7	1	
50	7/7	18	
37.5	Continuous	3	21 patients (20.6%) reduced to 37.5 mg (36–63% in randomized trials)[2,18,31,32]
37.5	14/7	8	
37.5	11/7	2	
37.5	9/7	2	
37.5	7/7	6	
25	Continuous	3	7 patients (6.8%) reduced to 25 mg (27–43% in in randomized trials)[2,18,31,32]
25	14/7	2	
25	7/7	2	

Changing the schedule from four/two to two/one may not optimize dose intensity for all patients

Several retrospective and two small prospective studies have suggested that the two-weeks-on/one-week-off schedule (two/one) may improve the therapeutic index for sunitinib vs. the standard four/two schedule.[20-24] Three ongoing prospective studies (NCT02060370, NCT02689167, and NCT02398552) will further evaluate the value of the two/one schedule.

It is important to note that based on the dose/schedule distribution (Table 1) in our individualization study, the two/one schedule was optimal in only 39 (37%) patients. Simply replacing one rigid schedule (four/two) with another (two/one) would lead to underdosing of over 60% of patients. The patients who could take a certain sunitinib dose for less than 14 days would be dose-reduced rather than given fewer days on drug, and patients who could take more than 14 days would have minimal toxicity and be underdosed. Starting therapy on the two/one schedule underdoses all the patients who can take 50 mg for more than 14 days, plus the 20% of patients who can be dose-escalated.

Following the schedule outline in Fig. 1 may allow patients to receive as much drug as possible with the degree of toxicity that is acceptable to them. One of the most gratifying experiences of using individualized dosing, both on and off this study, has been that patients understand this concept very well and many take over control of their therapy, adding days when they feel they can and stopping early if they feel their toxicity has reached the level they can accept.

What about other TKIs for metastatic RCC?

As is the case for sunitinib, an association between higher AUC and better outcome has been documented for pazopanib[25] and axitinib[26] and dose escalation may improve the activity of sorafenib.[27-29] Traditionally, these three drugs are given continuously without a break, with dose reductions if toxicity is encountered on continuous therapy. In an ongoing trial (NCT02579811), a more detailed dose individualization of axitinib is being studied where patients are treated to toxicity with planned breaks off therapy. It may be reasonable to assume that a TKI that can be given continuously with minimum toxicity is underdosed.

All oncologists individualize cancer therapy on a daily basis, but usually to a lower dose. Dose escalations are rare. Dose reductions and drug discontinuations are more common with oral than intravenous drugs because of the limited

Table 2. Response rate for 102 evaluable patients[19]

Study	OZM 42*	EFFECT	COMPARZ	
Drug	Individualized sunitinib dose	Sunitinib standard dose	Sunitinib	Pazopanib
n	102	146	553	557
CR %	3.9 (n=4)	0	<1	<1
PR %	44.1 (n=45)	32	24	31
CR + PR %	48.0 (n=49)	32	25	31
SD %	41.2 (n=42)	43	44	39
CR + PR + SD %	89.2 (n=74)	75	69	70
PD %	10.8* (n=11)	25	19	17

*44/102 (43.1%) evaluable patients still on therapy. CR: complete response; SD: stable disease; PD: progressive disease; PR: partial response.

dosing options if a rigid schedule is used for oral drugs.[30] Individualizing the duration of therapy provides another mechanism to modify the dose intensity of oral drugs more accurately. This is done in the current sunitinib individualization study described above.

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