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Treatment sequences in metastatic renal cell carcinoma (mRCC): efficacy results from the Czech registry (RENIS)

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BACKGROUND

Efficacy data of treatment sequences in mRCC are rare despite the worldwide use. In the Czech Republic, data on efficacy and safety of all targeted therapies for mRCC are collected in the RENIS patient registry.[1] Thus, RENIS provides unique data from the real-world clinical practice. The aim of this study was to compare outcomes of selected treatment sequences in mRCC while adjusting for differences in patient characteristics using inverse propensity score weighting method (IPWS).

Table 1. Baseline characteristics of original (weighted) sample by treatment sequence*

Treatment sequence		Sunitinib → Everolimus	Sunitinib → Axitinib	Sunitinib → Axitinib → Everolimus	Pazopanib → Everolimus	Pazopanib → Sunitinib
Variable		Original (Weighted) value				
Number of patients/ESS		312/309	154/140	114/106	74/68	91/75
Age at baseline: mean		63.2 (63.6)	62.4 (62.7)	61.0 (61.8)	65.9 (64.2)	66.5 (64.6)
Years between diagnosis and treatment initiation: mean		2.6 (2.8)	3.1 (2.8)	2.7 (2.7)	3.0 (2.9)	3.0 (2.8)
Gender: % male		76% (75%)	73% (72%)	77% (77%)	64% (64%)	70% (72%)
ECOG	% ECOG=0	40% (41%)	47% (41%)	39% (41%)	42% (41%)	38% (43%)
	% ECOG=1	60% (59%)	53% (59%)	61% (59%)	58% (59%)	62% (57%)
No nephrectomy: (%)		17% (15%)	10% (16%)	13% (16%)	9% (15%)	22% (14%)
Primary disease status at diagnosis:	Non-metastatic	50% (47%)	55% (44%)	59% (52%)	59% (50%)	44% (41%)
	Metastatic	50% (53%)	45% (56%)	41% (48%)	51% (50%)	56% (59%)
MSKCC	Favourable	30% (32%)	36% (32%)	32% (32%)	32% (32%)	27% (31%)
	Intermediate	64% (64%)	62% (63%)	62% (64%)	65% (65%)	68% (65%)
	Poor	5% (4%)	2% (5%)	5% (4%)	3% (3%)	4% (3%)
Karnofsky score	≤70%	7% (7%)	3% (3%)	5% (5%)	5% (5%)	7% (7%)
	80%	23% (23%)	18% (22%)	27% (29%)	22% (20%)	26% (25%)
	90%	47% (46%)	58% (56%)	42% (39%)	51% (54%)	45% (42%)
	100%	23% (23%)	21% (19%)	25% (27%)	22% (21%)	22% (26%)
Primary tumor grade**	G1	6% (5%)	8% (8%)	8% (8%)	8% (8%)	7% (6%)
	G2	31% (31%)	32% (34%)	32% (32%)	53% (51%)	31% (30%)
	G3-4	47% (47%)	44% (44%)	46% (47%)	28% (29%)	50% (54%)
	GX	16% (17%)	15% (15%)	15% (14%)	11% (10%)	12% (9%)

*For example, in sunitinib→everolimus arm, the mean age is equal to 63.2 years; after IPWS, the mean age is equal to 63.6.
**G1=well differentiated; G2: moderately differentiated; G-4 poorly differentiated/undifferentiated; GX: grade cannot be assessed.
ESS: effective sample size.

Table 2. Results of OS and PFS for examined sequences computed using inverse propensity score weighting

Parameter	Treatment sequence	n	Median	95% CI for median		Mean	p
				Lower limit	Upper limit		
OS (months)	Sunitinib → Everolimus	312	26.3	23.8	29.0	33.3	<0.001
	Sunitinib → Axitinib	154	47.6	31.3	50.5	44.6	
	Sunitinib → Axitinib → Everolimus†	114	46.0	44.7	50.9	49.2	
	Pazopanib → Everolimus	74	32.9	30.9	33.8	40.7	
	Pazopanib → Sunitinib	91	27.2	26.7	28.8	40.6	
PFS 1st line (months)	Sunitinib	580	10.2	9.8	10.8	14.8	0.44
	Pazopanib	165	9.2	8.5	10.0	13.7	
PFS 2nd line** (months)	Sunitinib → Everolimus	312	5.8	5.1	6.3	10.1	0.035
	Sunitinib → Axitinib	268	6.4	6.0	7.1	11.1	
	Pazopanib → Everolimus	74	5.1	4.1	5.5	13.2	
	Pazopanib → Sunitinib	91	5.3	5.1	7.1	15.1	

*OS = overall survival, PFS = progression free survival, CI = confidence interval, n = number of included patients.
†Sunitinib → Axitinib → Everolimus should be assessed with caution due to immortal time bias.**This means: everolimus administered in 2nd line after sunitinib in the 1st line, axitinib after sunitinib, everoliums/sunitinib after pazopanib.

METHODS

- Data of mRCC patients treated using most common treatment sequences were collected in RENIS between June 2007 and February 2018.
- Overall survival (OS) and progression free survival (PFS) were collected as main outcomes.
- Variables used were grouped to have reasonable number of patients in each group in each cohort. Examined variables were years from the diagnosis to start of treatment, Karnofsky score (categories 70% and less, 80%, 90%, 100%), performance of nephrectomy (partial and total nephrectomy vs. no nephrectomy), primary tumor grade (grades 3 and 4 grouped together), Memorial Sloan-Kettering Cancer Center (MSKCC) score, age (categories less than 60 and more than 60), gender, primary disease status (categories localized/locally advanced and primary metastatic disease) and Eastern Cooperative Oncology Group performance status (ECOG groups =0 and >0).
- Effects of baseline characteristics on OS were estimated using Cox proportional hazards (PH) multivariate model.
- Cohorts were balanced for baseline characteristics using IPWS. The propensity score was evaluated with multinomial logistic model to balance ECOG, time from diagnosis to first treatment, nephrectomy, MSKCC score, and age. These variables had highest effect on OS based on previous estimation using Cox PH model, clinical relevance and overall model performance (Akaike information criteria (AIC), significance of covariates, secondary interactions, hierarchicity, collinearity).[2,3,4]
- For the weighting, combined weights were used. For each cohort, weight was taken as inverse of propensity score for a particular cohort. Combined weights then could be interpreted asapproximately average population of all included patients in all cohorts.
- On the weighted data, OS, PFS of 1st line treatment and PFS of 2nd line treatment were evaluated. Median and 95 % confidence intervals (CI) were derived from IPWS weighted Kaplan-Meier curves that were compared usingoverall log-rank test. Also, restricted mean OS/PFS (henceforth mean) was presented using limit of 78.4 months for OS, 70.6 months for PFS on 1st line and 50.2 months for PFS on 2nd line treatment. The OS/PFS limits were based on the last data point observed. Mean OS/PFS was calculated based on presented K-M curves.

RESULTS

- In total, 745 (out of 746) patients in five treatment sequences were included and analyzed (sunitinib→pazopanib sequence was excluded due to a small study sample; n=15).
- The effective sample size (ESS) shows that the number of patients in each arm did not decrease after the weighting (**Table 1**). This means that there is a very high similarity between studied sequences and thus high mutual overlap (see original unweighted characteristics of patients (**Table 1**)). IPWS is thus appropriate method to adjust for population differences.
- **Table 1** shows baseline characteristics of original (i.e. unweighted) and weighted cohort. We can see very high similarity of weighted cohort among all sequences. Complete balance was not achieved, since multiple covariates and their interactions were included to model multiple levels (cohorts) as explained variable, thus final propensity score model is very complicated. However, balanced characteristics approached as well as the ones that were excluded from balancing, which shows good performance of IPWS.
- Years from onset to baseline, Karnofsky score, performance of nephrectomy and primary tumor grade significantly affect OS (p<0.05), MSKCC score is nearly significant (p=0.06). Accounting for previously mentioned variables, age, gender, primary disease status and ECOG does not affects OS significantly, yet these variables were included to allow relevant comparison of all cohorts.
- Differences in OS were statistically significant (p <0.001) with highest median OS of 46.0 months for sunitinib→axitinib→everolimus sequence and 47.6 months for sunitinib→axitinib sequence (**Figure 1** and **Table 2**). Other sequences showed worse OS.
- Sunitinib→axitinib→everolimus should be interpreted with caution because it is obviously affected by patients who naturally lived longer and were suitable for 3rd line therapy. Also, axitinib was introduced later than other therapies, which may have influenced the results (i.e. better general healthcare over time, introduction of new therapies etc.).
- PFS in the 1st line did not differ significantly between sunitinib and pazopanib (p=0.44) (**Figure 2**).
- PFS in the 2nd line differed significantly (p=0.035) with median ranging from 5.1 for Pazopanib→everolimus (i.e. everolimus administered after pazopanib in the 1st line) arm to 6.4 months for sunitinib→axitinib cohort (**Figure 3** and **Table 2**). Obviously, previous line has a potential treatment effect on the subsequent line and therefore we accounted for this factor.

Figure 1. Overall survival after weighting

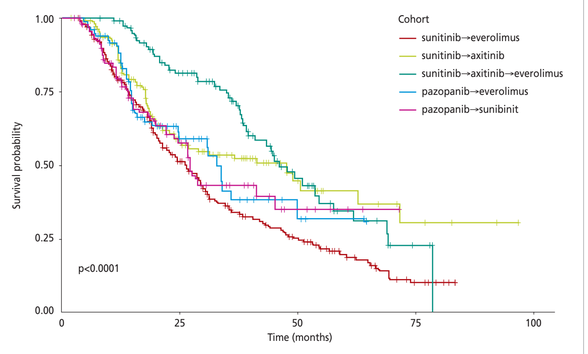


Figure 2. Weighted 1st line progression-free survival

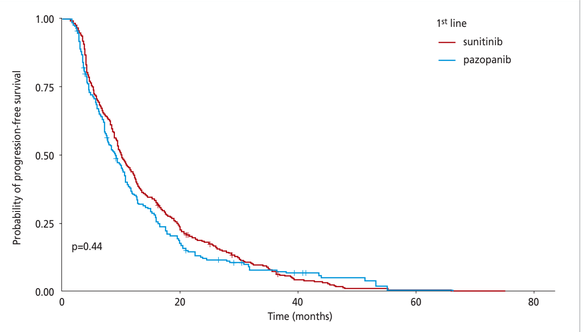
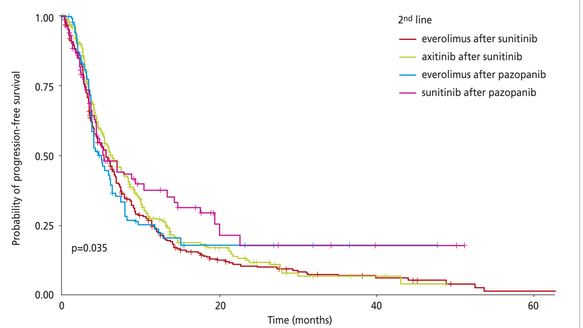


Figure 3. Weighted 2nd line progression-free survival



CONCLUSIONS

This study analyzes efficacy (OS/PFS) of common treatment sequences in mRCC patients on an extensive and well-described cohort of patients. Sequences containing sunitinib→axitinib seem to outperform other sequences commonly used. Improved outcome of sequences with second-line axitinib over those using second-line sunitinib or everolimus in the cohort of patients from a national registry could be also be explained by the time when these drugs were introduced. Nevertheless, IPWS models balances characteristics, but does not substitute for "proper" randomization and double-blinding.

REFERENCES

1 RENIS registry (http://renis.registry.cz/). • 2 McCaffreyDFStat in Med. 2013;32(19):3388-3414. • 3 Faria R,NICE DSU technical support document. NICE, 2015. 85 p. • 4 Li F. (2014). Balancing Covariates via Propensity Score Weighting.

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