A model-based analysis for first-line treatment of metastatic Renal cell carcinoma: Implications from the perspective of AB PM-JAY

Health Technology Assessment in India (HTAIn)
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Policy Brief

Executive Summary:

Renal cell carcinoma (RCC) accounts for 3% of all adult cancers and 85% of all kidney tumours (1). The incidence of RCC has been reported to be about 2 per 100,000 and 1 per 100,000 among males and females respectively in India (2). It is more common among the elderly with median age of presentation ranging from 50-60 years with clear cell carcinoma being the commonest histological type accounting for 70-80% of RCC (3).

In this analysis, we aimed to determine the most cost-effective treatment option for newly diagnosed metastatic RCC (mRCC) patients in India. Using a Markov model, the clinical effectiveness and costs of monotherapies (either Sunitinib, or Pazopanib) and combination therapies (either Pembrolizumab/Lenvatinib, or Nivolumab/Ipilimumab) were estimated. Incremental cost per QALY gained with a given treatment option was compared against the next best alternative, and assessed for cost-effectiveness. Sunitinib incurs an average cost of ₹ 143,269 ($ 1,939) per QALY lived which has a 94.6% probability of being cost-effective at the willingness to pay threshold of 1-time per capita GDP in the Indian context. The immunotherapeutic agents such as Nivolumab, Pembrolizumab are not cost-effective at the current prices in India.

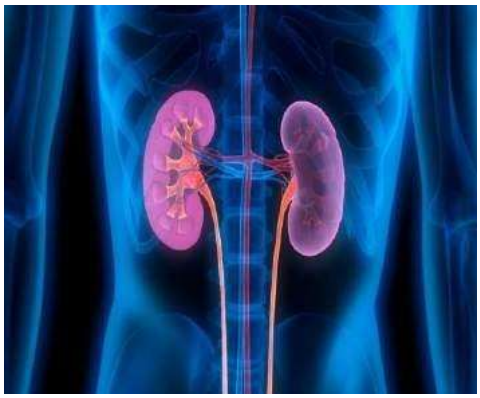


Image source: Internet

Policy Recommendations:

- From the perspectiveof current reimbursement rates,sunitinib is a cost-effective treatment option for first-line metastatic renal cell carcinoma patients in India.
- The use of combination therapies are currently not value for money in the Indian context.
- Further research on the effectiveness and application of these agents among various subgroups should be done.

Background and Gap in Literature:

National Cancer Grid (NCG) and Evidence-based Management (EBM) guidelines recommend the use of Tyrosine-kinase Inhibitors (TKIs) such as Sunitinib and Pazopanib as the first-line therapy for favourable-risk metastatic RCC patients. The high price of these agents in the Indian context made it unaffordable for majority cancer patients. However, the introduction of low-cost generics in the Indian market has provided some relief to the Indian mRCC patients. Moreover, India's government funded health insurance program - the Ayushman Bharat Pradhan Mantri Jan Aarogya Yojana (PM-JAY) has recently included various targeted therapies (such as sunitinib, cabozantinib and sorafenib) for the treatment of mRCC in its health benefit package (HBP). This has helped in reducing the financial hardship currently being faced by many Indian patients. The CHECKMATE-214 and CLEAR clinical trial paved the way for the use of Immune checkpoint inhibitors (ICIs) such as pembrolizumab and nivolumab in combination with TKIs (4,5). This combination has shown significant improvement in both progression free survival (PFS) and overall survival(OS), with less toxicities as compared to the conventional sunitinib monotherapy. However, the newer ICIs are presently expensive both in the Indian and global markets. Therefore, the cost-effectiveness analysis has an important role, especially in the low-middle income countries such as India, in helping the physicians and payers in choosing appropriate therapy which represents value for money.

Aims and Objective

This policy brief addressed the policy question of the most cost-effective treatment option for newly diagnosed RCC patients from the point of view of reimbursement rates set under AB PM-JAY scheme. It summarizes the results of a Economic evaluation study on various RCC treatment regimens, conducted by the HTA Resource Hub, PGIMER, Chandigarh.

Treatment arms:

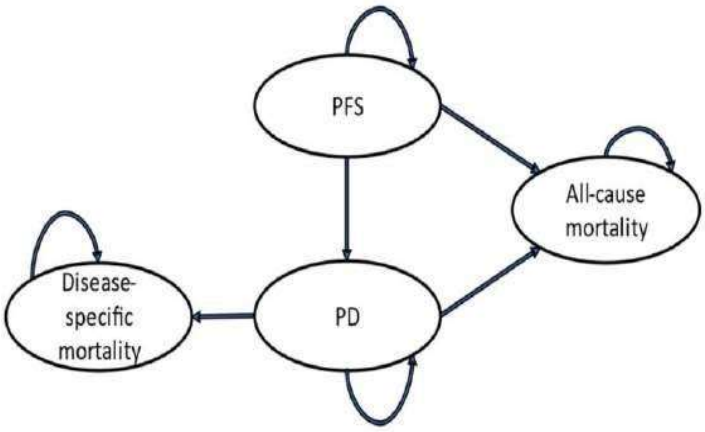
1. Sunitinib (50 mg orally once daily for 4 weeks of treatment followed by 2 weeks with no treatment);
2. Pazopanib (800 mg orally once daily);
3. Pembrolizumab (200 mg intravenously 3-weekly) plus Lenvatinib (20 mg orally once daily);
4. Nivolumab (240 mg intravenously 2-weekly) plus Ipilimumab 50 mg (4 doses intravenously once every6 weeks)

Methods and Approach

We undertook this cost-effectiveness analysis (CEA) using a societal perspective, which accounted for both health system and patients' costs. We compared the costs and consequences associated with sunitinib, pazopanib, combination of pembrolizumab/Lenvatinib and nivolumab/ipilimumab . Our methodological principles are consistent with the Indian reference case for conducting economic evaluations used by the agency for Health Technology Assessment in India (HTAIn).

The analysis was performed under the following components:

1. **Markov model** was developed in Microsoft Excel to estimate the lifetime costs and consequences (in terms of Quality Adjusted Life-years (QALYs)* and Life-years). The model consisted of three mutually exclusive health states: Progression-free survival (PFS), Progressive disease (PD) and death. A 6-weekly cycle length based on the treatment schedule of the sunitinib treatment arm was considered (Figure 1).
2. Reimbursement rates (for sunitinib, and sorafenib) and market prices (pazopanib, pembrolizumab, lenvatinib, nivolumab, ipilumumab and axitinib) were used to estimate the treatment cost in each health state.
3. In order to obtain the Out-of-Pocket Expenditure (OOPE) incurred on out-patient consultations, the primary data was analysed as a part **CADCQoL database** (7).
4. Transition probabilities and effectiveness parameters were obtained from the pivotal clinical trials and systematic reviews and network meta-analysis (4,5,6).
5. The Quality of Life (QoL) scores were estimated from the published studies (8).



transition model. PFS: Progression-Free State; PD: Progressive Disease

*Quality Adjusted Life-years:

- QALY is a generic measure of health and is usedto compare the health gains across different diseases and hence provide a uniform platformto compare effectiveness across all the different areas of healthcare.
- EQ5D is the most utilised tool worldwide to measure QoL.

Treatment strategy	Cost in ₹	QALYs	Incremental cost per QALY gained in ₹	Interpretation
Sunitinib	273,846	1.91	-	ND
Nivolumab / Ipilimumab	6,686,526	1.97	115,885,317	ND
Pembrolizumab / Lenvatinib	9,744,330	2.75	3,953,457	ND
Pazopanib	348,537	1.86	-	D

Results:

- Sunitinib is the most cost-effective treatment option and incurs an average cost of ₹ 143,269 ($ 1,939) per QALY lived in the Indian context.
- At the current WTP threshold of one-time per capita GDP (₹ 168,300) of India, sunitinib has 94.6% probability of being cost-effective.
- Pazopanib is a dominated treatment strategy in the Indian context as it offers similar health outcomes at a significantly higher cost than sunitinib.
- None of the combination therapies are cost-effective at the current WTP threshold of 1-time per capita GDP of India.

References:

1. Ljungberg B, Campbell SC, Choi HY, Cho HY, Jacqmin D, Lee JE, et al. The epidemiology of renal cell carcinoma. Eur Urol. 2011 Oct;60(4):615–21.
2. Abraham GP, Cherian T, Mahadevan P, Avinash TS, George D, Manuel E. Detailed study of survival of patients with renal cell carcinoma in India. Indian J Cancer. 2016 Oct 1;53(4):572.
3. Pallagani L, Choudhary GR, Himanshu P, Madduri VKS, Singh M, Gupta P, et al. Epidemiology and Clinicopathological Profile of Renal Cell Carcinoma: A Review from Tertiary Care Referral Centre. J Kidney Cancer VHL. 2021 Jan 20;8(1):1–6
4. Motzer RJ, Tannir NM, McDermott DF, Arén Frontera O, Melichar B, Choueiri TK, et al. Nivolumab plus Ipilimumab versus Sunitinib in Advanced Renal-Cell Carcinoma. N Engl J Med. 2018 Apr 5;378(14):1277–90
5. Motzer R, Alekseev B, Rha SY, Porta C, Eto M, Powles T, et al. Lenvatinib plus Pembrolizumab or Everolimus for Advanced Renal Cell Carcinoma. N Engl J Med. 2021 Apr 8;384(14):1289–300
6. Motzer RJ, Hutson TE, Cella D, Reeves J, Hawkins R, Guo J, et al. Pazopanib versus Sunitinib in Metastatic Renal-Cell Carcinoma. http://dx.doi.org/10.1056/NEJMoa1303989. Massachusetts Medical Society; 2013
7. Prinja S, Dixit J, Gupta N, Mehra N, Singh A, Krishnamurthy MN, et al. Development of National Cancer Database for Cost and Quality of Life (CaDCQoL) in India: a protocol. BMJ Open. 2021 Jul 1;11(7):e048513
8. de Groot S, Redekop WK, Versteegh MM, Sleijfer S, Oosterwijk E, Kiemeney LALM, et al. Health-related quality of life and its determinants in patients with metastatic renal cell carcinoma. Qual Life Res. 2018;27(1):115–24