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Title Sunitinib/ Pazopanib as First-Line Treatment and Axitinib/ Everolimus as Second-Line Treatment for Metastatic Renal Cell Carcinoma and Economic Evaluation

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Aim

To evaluate the evidence on effectiveness, safety and cost-effectiveness of sunitinib/ pazopanib as first-line treatment and axitinib/ everolimus as second-line treatment for metastatic renal cell carcinoma (mRCC).

Conclusions and results

Part 1: Systematic review of literature

A. Sunitinib

Effectiveness

1) Conventional 4/2 dosing schedule

Good level of retrievable evidence to suggest that sunitinib:

- Sunitinib was superior to interferon-alpha, bevacizumab plus interferon alpha, everolimus, sorafenib, as well as temsirolimus plus bevacizumab, and has comparable outcomes with pazopanib, axitinib and tivozanib in terms of progression-free survival, as first-line treatment in patients with mRCC
- Sunitinib has comparable overall survival to pazopanib and better overall survival compared to interferon-alpha alone
- Sunitinib and pazopanib had better response rates than bevacizumab with interferon
- Sunitinib was found to have led to better HRQoL compared to interferon-alpha while pazopanib was associated with better HRQoL compared to sunitinib

Insufficient evidence to recommend the use of sunitinib in non-clear cell RCC and the available data suggested that it was less effective compared to that in advanced clear cell RCC.

Good level of retrievable evidence to suggest that the use of sunitinib as first-line treatment in metastatic renal cell carcinoma was safe with no statistically significant difference found in terms of serious adverse events rates when compared with pazopanib. The most commonly reported adverse events and laboratory abnormalities in the sunitinib group were diarrhoea, fatigue, nausea, hand–foot syndrome, leukopenia, neutropenia, anaemia, increased creatinine, thrombocytopenia and lymphopenia.

2) Conventional 4/2 dosing versus 2/1 dosing schedule

Limited fair level of retrievable evidence to suggest that:

- There was no significant difference in tumour response, median overall survival and time to progression between
- 2/1 dosing schedule was associated with higher failure-free survival at six months and longer time-to-treatment failure than the conventional 4/2 dosing schedule
- 2/1 dosing schedule was associated with better HRQoL compared to the conventional dosing.

Fair to good level of retrievable evidence to suggest that neutropenia, fatigue, diarrhoea and hand-foot syndrome were more frequent with schedule 4/2 than with schedule 2/1. No significant difference between groups in the incidence of adverse events at Grade 3 or higher.

3) Attenuated dosing schedule

Limited fair level of retrievable evidence to suggest that:

- No significant difference in the overall survival and progression-free survival between the attenuated dosing of sunitinib and conventional 4/2 dosing schedule
- Associated with lower incidence of severe toxicities (Grade 3 or higher), dose delays and dose reductions during the course of treatment

4) Continuous dosing schedule

Limited fair level of retrievable evidence to suggest that:

- No significant difference between the two schedules in the overall survival and progression-free survival, however, the conventional 4/2 dosing was associated with longer time to deterioration and decrease kidney related symptoms compared to the continuous dosing schedule
- No significant difference between continuous dosing schedule and conventional 4/2 dosing schedule of sunitinib in terms of the incidence of any-grade or grade 3 to 4 adverse events and laboratory abnormalities

Cost-effectiveness

Based on the cost-utility analyses, sunitinib was a cost-effective therapy option compared to bevacizumab plus interferon-alfa, interferon-alfa, interleukin-2 and

interleukin-2 plus interferon-alfa, when the willingness-to-pay threshold is higher than USD$16,000. However using three times GDP per capita of China as recommended by WHO yielded threshold of USD$13,290. Based on the analyses, sunitinib was found to be less cost-effective when compared to pazopanib. The results were found to be sensitive to the utility values and costs of treatment.

B. Pazopanib

Effectiveness

Based on the limited good level of evidence retrieved, patients on pazopanib had significantly longer progression free survival (PFS) than placebo, 11.1 months vs. 2.8 respectively with a hazard ratio (HR) of 0.40 (95% CI: 0.27, 0.60). However, when compared to sunitinib, there was no significant difference in terms of effectiveness [PFS of 8.4 vs. 9.5 months, HR 1.05 (5%CI: 0.90, 1.22)], quality of life, persistence and compliance. Nevertheless, in terms of preference, there were significantly more patients and physicians preferring pazopanib. Patients who received pazopanib had significantly less utilisation of services in terms of telephone consultation and emergency department visit.

Pazopanib and sunitinib had similar rate of dose reduction and drug discontinuation due to adverse events. However, their safety profiles differed. Elevation in liver function tests, weight loss, and changes in hair colour were more common with pazopanib whereas fatigue, hand-foot and mouth syndrome and mouth sores were more common with sunitinib.

Cost-effectiveness

As for cost-effectiveness, pazopanib was shown to provide more QALYs at a lower cost and dominant when compared to sunitinib.

C. Axitinib

Effectiveness

There was limited good level of retrievable evidence to suggest that compared to sorafenib, axitinib resulted in significantly longer median progression free survival (PFS) (6.7 months for axitinib versus 4.7 months for sorafenib; hazard ratio 0.665 [95% CI: 0.544, 0.812]), had comparable effect on patient-reported kidney-specific symptoms and health status, and showed no difference in median overall survival (OS) (axitinib 20.1 months [95% CI 16.7, 23.4], sorafenib 19.2 months [95% CI: 17.5, 22.3], HR 0.969, [95% CI: 0.800, 1.174]).

There was limited fair level of retrievable evidence that showed no statistical difference between patients treated with everolimus compared to those treated with axitinib for OS (HR 1.02; 95% CI: 0.67, 1.55) or PFS (HR 1.07; 95% CI: 0.70, 1.64).

The most frequent adverse events reported which was associated with axitinib were diarrhoea, hypertension, fatigue, decreased appetite, nausea, and dysphonia, while palmar-plantar erythrodysaesthesia, alopecia, and rash were more common with sorafenib. The most common adverse events of grade 3 or higher or laboratory abnormalities with axitinib were hypertension, diarrhoea, and fatigue. The occurrence rate of treatment-emergent, all causality hypertension, grade 3 hypertension, and hypertensive crisis were generally higher in axitinib-treated patients compared to sorafenib-treated patients. Rates of individual hypertension–related sequelae (transient ischemic attack [TIA], hypertensive crisis, angina pectoris, cerebral haemorrhage, cerebrovascular accident [CVA], and leukoencephalopathy) in axitinib-treated patients were generally low (<1%).

Cost-effectiveness

A cost-effectiveness analysis conducted in Cyprus found that the estimated incremental cost-effectiveness ratio (ICER) per QALY of axitinib compared to sorafenib was €87,936. The cost-effectiveness acceptability curve suggested that the probability of axitinib to be cost-effective at the threshold of €60,000 was 13%.

An economic analysis conducted in the US demonstrated that patients with sunitinib-refractory advanced RCC who were treated with everolimus had an average lifetime costs of $104,226, compared to $117,211 for patients treated with axitinib. Thus, patients treated with everolimus cost an average of $12,985 (11%) less over their lifetimes than patients treated with axitinib.

D. Everolimus

Effectiveness

There was limited good level of retrievable evidence to suggest that compared with placebo, everolimus resulted in significantly longer progression free survival (PFS) (4.9 months with everolimus versus 1.9 months with placebo; hazard ratio [HR] 0.33; 95% Confidence Interval [CI]: 0.25, 0.43; P<0.001), but no difference in overall survival (OS) (14.8 months with everolimus versus 14.4 months with placebo; HR 0.87; 95% CI: 0.65, 1.15; P=0.162). In terms of patient-reported outcomes, there was no difference in disease-related symptoms, and only small, although statistically significant, differences in physical functioning and global quality of life.

There was fair level of retrievable evidence to suggest that compared to temsirolimus, everolimus resulted in significantly better OS and time to treatment failure (TTF).

The reported most frequent adverse events (AE) associated with everolimus were stomatitis, infections, fatigue, aesthenia, diarrhoea, cough and non-infectious pneumonitis. Stomatitis was the most common adverse events of any grade in everolimus-treated patients, including in the elderly population. Some AE including peripheral edema, cough, rash and diarrhoea occurred at higher rates in the elderly population in both the everolimus and placebo treatment groups compared with the overall study population. However, grade 3 or 4 AE in this sub-group were low and consistent with the rates reported in the total population.

Cost-effectiveness

A cost-effectiveness analysis conducted in US demonstrated that the estimated incremental cost-effectiveness (ICER) for everolimus compared to sorafenib was $64,155/LYG or $89,160/QALY. The cost-effectiveness acceptability curve showed that the probability of the ICER to fall below $70,000/ QALY, $80,000/ QALY and $90,000/QALY was 15.8%, 68.3% and 98.0%, respectively.

An economic evaluation conducted in Serbia showed that the ICER for everolimus treatment compared to best supportive care was estimated at €65,926/ LYG or €86,978/ QALY. The cost-effectiveness acceptability curve revealed that the probability everolimus to be cost-effective was 54% when the threshold was put at the base-case ICER estimate of €86,978/ QALY.

An economic analysis conducted in US demonstrated that patients with sunitinib-refractory advanced RCC who were treated with everolimus had an average lifetime costs of $104,226, compared to $117,211 for patients treated with axitinib. Thus, patients treated with everolimus cost an average of $12,985 (11%) less over their lifetimes than patients treated with axitinib.

Part 2: Economic evaluation

Based on the above analysis, pazopanib and sunitinib have considerably comparable average healthcare cost per patient as first line treatment for metastatic renal cell carcinoma. Attenuated dosing schedule was shown to be the most cost saving treatments with relatively fair differences compared with pazopanib; subjected to the limited retrievable evidence. However, the selection of treatment mix may depend on the clinical judgement of the patient's suitability and affordability of the healthcare provider.

Everolimus and axitinib as second line treatment of metastatic renal cell carcinoma are significantly effective but more expensive compared with best supportive care alone. Everolimus may be considered to be cost-effective as a second line treatment for metastatic renal cell carcinoma at the suggested value of cost-effectiveness threshold by World Health Organization (WHO) (1-3 Gross Domestic Product (GDP) per capita) with base case incremental cost-effectiveness ratio (ICER) of RM 84,595.93 per QALY gained. However, if suggested cost-effectiveness threshold for Malaysia is taken into consideration which is ≤ 1 GDP per capita, this treatment may not be a cost-effective strategy. Meanwhile, axitinib is considered not to be cost-effective at the suggested value of cost-effectiveness threshold by WHO (1-3 GDP per capita) and suggested cost-effectiveness threshold for Malaysia which is ≤ 1 GDP per capita with base case incremental cost-effectiveness ratio (ICER) of RM 290,055.87 per QALY gained.

Bigger magnitude of ICER changes from base case results were found to be related to utility value, costs and clinical parameters, while discount rate may not significantly affect the ICERs.

Recommendations (if any)

Sunitinib/ pazopanib may be use as first line treatment and everolimus / axitinib may be use as second line treatment for metastatic renal cell carcinoma. However, affordability remains as an important issue.

Methods

Literature search was done to search for published articles to assess the effectiveness, safety and cost-effectiveness of sunitinib as first line treatment for metastatic renal cell carcinoma. The following electronic databases were searched via OVID Interface: MEDLINE (1946 to present), EBM Reviews-Cochrane Database of Systematic Reviews (2005 to July 2016), EBM Reviews-Cochrane Central Register of Controlled Trials (July 2016), EBM Reviews–Database of Abstracts of Review of Effects (3rd Quarter 2016), EBM Reviews-Health Technology Assessment (3rd Quarter 2016) NHS economic evaluation database (1st Quarter 2016), PubMed and INAHTA database. Google was used to search for additional web-based materials and information. Additional articles were identified from reviewing the references of retrieved articles. The last search was run on 25th June 2016.

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