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HEALTH AND CLINICAL EXCELLENCE

Temsirolimus (Torisel*)

Appraisal of the clinical and cost-effectiveness of temsirolimus for the first-line treatment of patients with advanced renal cell carcinoma who have at least three of six prognostic risk factors

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Executive Summary

Advanced renal cell carcinoma (aRCC) is a cancer of the kidney associated with lymph node involvement and metastases to distant organs. Mortality from kidney cancer continues to rise in the UK(1) and patients with aRCC and three or more prognostic risk factors have the poorest prognosis with a median survival of 7.3 months and a 1-year survival rate of 23% (2).

Although kidney cancer is the eighth and fourteenth most common cancer in men and women respectively (1) poor prognosis aRCC accounts for less than 7% of all kidney cancers. Thus of the estimated 7,144 new cases of kidney cancer per year in the UK only 450 will be poor prognosis aRCC. At less than 1,000 patients in the UK this constitutes what NICE has termed an ultra-orphan condition.

Effective therapeutic options are very limited and current treatments have no documented impact on overall survival in these patients. The effectiveness of immunomodulatory therapy with interferon alfa (IFN-α), the standard of care in the UK, is limited by its tolerability and provides little benefit to patients with extensive tumour burden and adverse prognostic factors(3). In particular IFN-α is ineffective in non-nephrectomised patients and those with non-clear cell histology. Clearly there is a substantial unmet clinical need for an effective and well-tolerated treatment for poor prognosis aRCC.

Temsirolimus (Torisel) is a new and innovative therapy, the first cancer agent to act by inhibiting the mammalian target of rapamycin (mTOR) kinase. mTOR is a serine/threonine kinase that regulates both cell growth and proliferation and angiogenesis(4). Given that angiogenesis is a clinical feature of RCC, it is likely that this additional mode of action of temsirolimus contributes to its superior efficacy over immunomodulatory therapy. Torisel, which has been granted orphan drug status, has a marketing authorization within the EU for the first line treatment of patients with aRCC who have at least three of six prognostic factors.

In the pivotal Phase III randomised trial of 626 patients with previously untreated, poor prognosis aRCC, temsirolimus treatment demonstrated a 49% increase in median overall survival (OS) compared with IFN-α monotherapy (10.9 months vs 7.3 months), with a hazard ratio for death of 0.73 (95% CI, 0.58 – 0.92; p=0.0078) and a 77% increase in median progression-free survival (PFS) (5.5 months vs 3.1 months) with a hazard ratio for progression of 0.66 (95% CI, 0.53 – 0.81; p=0.0001). The

benefit of temsirolimus over IFN-α was greatest in patients with non-clear cell histologies and those who had not undergone prior nephrectomy (5).

Temsirolimus is better tolerated than IFN-α. Fewer patients treated with temsirolimus reported Grade 3 or 4 adverse events compared with those treated with IFN-α (67% vs 78% respectively; p=0.02), this despite greater dose reductions and dose delays in patients receiving IFN-α. Whilst patients treated with temsirolimus received 92% of their planned maximum dose, IFN-α patients received just 56% of the planned dose(5).

An analysis of the time patients spend in different health states (with severe toxicity, with disease progression and time without symptoms or toxicity (TWiST)) demonstrated that patients treated with temsirolimus had a significantly greater time (38%) without symptoms or toxicity (6.50 months vs 4.70 months; p=0.005) compared with patients treated with IFN-α. Indeed the mean difference in overall survival was entirely accounted for by time spent without disease progression or toxicity(6).

A Markov model with three primary health states (first line progression-free, post progression and death) has been produced in Microsoft Excel. The cost effectiveness analysis was undertaken from an NHS perspective hence only direct health care costs are included. The results are presented in terms of incremental cost per life year (LY) gained and the incremental cost per quality adjusted life year (QALY). The model compares temsirolimus treatment with IFN-α. The principal data source for the model was the Phase III trial, which is used to inform the clinical parameters. Clinician opinion was used to determine resource use, unit cost data from standard UK sources was assigned to the resource use. The model follows patients for a maximum period of 36 months since by this time most patients are expected to have died.

Over the three-year period, compared with IFN-α treatment, temsirolimus resulted in an additional 0.211 LYs at a cost of £7,493 leading to an estimated cost per LY gained of £35,577. Quality adjusted incremental survival, using utilities derived from the clinical trial, resulted in 0.134 QALYs and an incremental cost per QALY of £55,814. The corresponding incremental cost effectiveness ratios (ICERs) for the subgroups of patients with non-clear cell histology and who had not undergone prior nephrectomy were £29,035 and £29,792 per LY gained and £51,159 and £49,690 per QALY gained respectively.

Whilst these estimates are above the threshold range currently applied to conventional appraisals they are below the ICERs that NICE estimates for existing ultra-orphan drugs on the UK market(7). Given the Citizens Council conclusions and the judgement of the Institute's board that there is public support for the NHS to meet the reasonable treatment costs of expensive treatments for ultra-orphan drugs, the use of temsirolimus to treat poor prognosis aRCC should be considered an appropriate use of NHS resources.

An estimated 238 poor prognosis aRCC patients will be eligible for temsirolimus treatment in England and Wales annually. Assuming all patients are treated the drug and administration costs are estimated to be £2,570,000 per annum.

In conclusion, temsirolimus significantly increases progression-free and overall survival in aRCC patients with the poorest prognosis. The drug is also better tolerated than IFN-α, the current standard of care in the UK, resulting in improvements in the quality as well as the quantity of life of these patients. Estimates of the cost effectiveness of temsirolimus in the treatment of poor prognosis aRCC indicate that it may be lower than treatments for other ultra-orphan conditions. Given the degree of clinical unmet need it would be appropriate to recommend the use of temsirolimus as first-line treatment for poor prognosis aRCC as recommended by the European Association of Urology's Guideline on Renal Cell Carcinoma(8).

References

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