Radium-223 dichloride in prostate cancer: Major added benefit for certain patients

April 3 2014

Radium-223 dichloride (radium-223 for short, trade name: Xofigo) has been approved since November 2013 for men with advanced prostate cancer, in whom hormone blockade is no longer effective, and symptomatic bone metastases, but without visceral metastases. In an early benefit assessment pursuant to the Act on the Reform of the Market for Medicinal Products (AMNOG), the German Institute for Quality and Efficiency in Health Care (IQWiG) examined whether this new drug offers an added benefit over the appropriate comparator therapy specified by the Federal Joint Committee (G-BA).

No evaluable data were available for the comparison with docetaxel in patients in whom prolongation of life was the primary treatment goal. Hence an added benefit is not proven for this comparison.

Depending on the patients' age and the concomitant treatment (with/without bisphosphonates), there is an indication of major and an indication of minor added benefit of radium-223 compared with best supportive care (BSC).

No valid data for the comparison with docetaxel combination therapy

Radium-223 dichloride is radioactive and mainly accumulates in the bone. By emitting radiation from nearby areas, the drug aims to inhibit bone metastases. The drug should not be used if additional metastases

have formed in the organs. The radiation poses no risk for other people.

If prolongation of life was the primary therapeutic objective and the patients were eligible for docetaxel treatment, the G-BA specified docetaxel in combination with prednisone or prednisolone as appropriate comparator therapy (docetaxel population). However, there were no evaluable data for this comparison. Hence an added benefit of radium-223 is not proven for this subpopulation.

BSC as comparator therapy for the treatment goal "symptom control"

If docetaxel treatment was not an option for the patients or if the primary treatment goal was the relief of symptoms, the so-called "symptom control", and the prevention of complications, the G-BA specified BSC as appropriate comparator therapy (BSC population). BSC means a therapy that provides the patient with the best possible individually optimized supportive treatment to alleviate symptoms and improve quality of life. In particular, these include adequate pain therapy, treatment with bisphosphonates and/or radionuclides.

Assessment based on approval study

The benefit assessment of radium-223 compared with BSC was the randomized controlled approval study BC1 06 (ALSYMPCA). 921 patients with an average (median) age of 70 to 71 years participated in this study worldwide. Two thirds of the patients received radium-223 + BSC, the others received placebo + BSC.

The majority of patients included in the study were not eligible for docetaxel because their disease had progressed despite pretreatment with this drug (approximately 57%). It was assumed in the assessment that

most of the remaining patients actively decided against docetaxel treatment. The study population was therefore an adequate approximation of the BSC population. Approximately 40% of the patients received concomitant treatment with bisphosphonates.

The BC1 02 study additionally cited by the drug manufacturer was not considered because radium-223 was not used in compliance with its approval in this study.

Uncertain results on side effects and quality of life

Data were available for the following outcomes: overall survival, time to first skeletal-related complication, adverse events and health-related quality of life. However, the results on severe and serious adverse events (e.g. pain), on discontinuation due to such events and on occurrence of diarrhoea were uncertain. The data on health-related quality of life presented by the manufacturer were either not evaluable (EQ-5D) or subject to great uncertainty (FACT-P).

Extent of survival advantage depends on age

Patients in the radium-223 arm of the study survived longer than patients in the control group, but the extent of added benefit depends on age: For men younger than 65 years, there was an indication of a major added benefit of radium-223. For patients aged over 65 years, only an indication of a minor added benefit could be determined.

Bone symptoms occurred later

Radium-223 also had advantages for the patients with regards to the burden of disease (morbidity). Bone symptoms occurred considerably later in men who were treated with radium-223 + BSC than under BSC

treatment alone. Concomitant treatment with bisphosphonates played a role for the extent of added benefit: For patients with bisphosphonate treatment, there was an indication of a major added benefit, whereas for patients without this concomitant treatment, there was only a hint of a non-quantifiable (no more than considerable) added benefit of radium-223 with BSC compared with BSC.

Fewer side effects in most patients

Most of the patients who were treated with radium-223 also had fewer side effects: With regards to serious/severe side effects, there were no more than indications of lesser harm from radium-223 + BSC compared with BSC with the extent of no more than "minor". This lesser harm was presumably due to side effects caused by an increased use of drugs (e.g. analgesics) in the placebo + BSC group.

This was offset by a hint of considerably greater harm from radium-223 + BSC due to more frequent, but never severe, diarrhoea in patients without docetaxel pretreatment. This greater harm did not raise doubts about the overall assessment.

Overall assessment: added benefit only for one patient population

Overall, there was an added benefit in the BSC population, which depended on age and concomitant bisphosphonate treatment: IQWiG determined an indication of a major added benefit of radium-223 + BSC versus BSC as appropriate comparator therapy in patients younger than 65 years and in patients older than 65 years who were treated with bisphosphonate. An indication of a minor added benefit of radium-223 can be derived for patients older than 65 years without concomitant bisphosphonate treatment.

In this overall assessment, the longer overall survival, the delay in the occurrence of bone symptoms and fewer side effects were decisive for the added benefit of radium-223 + BSC compared with BSC.

There were no evaluable data for the docetaxel population. Hence an added benefit of radium-223 is not proven for this subpopulation.

G-BA decides on the extent of added benefit

The dossier assessment is part of the overall procedure for early benefit assessments supervised by the G-BA. After publication of the manufacturer's dossier and IQWiG's assessment, the G-BA conducts a commenting procedure, which may provide further information and result in a change to the benefit assessment. The G-BA then decides on the extent of the added benefit, thus completing the early benefit assessment.

More information: An overview of the results of IQWiG's benefit assessment is given by a German-language executive summary. In addition, the website www.gesundheitsinformation.de , published by IQWiG, provides easily understandable and brief German-language information on radium-223 dichloride.

Provided by Institute for Quality and Efficiency in Health Care