Title	Bone Targeting Agents (BTAs) in Preventing Skeletal Related Events (SREs) for Metastatic Cancers of Solid Tumours Patients
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Reference	Health Technology Assessment Report, online: http://www.moh.gov.my/moh/penerbitan/mymahtas/HTA/HTA%20Bone%20Targeting%20Agents.pdf

Aim

To assess and compare the effectiveness, safety, economic implications, organizational or societal issues of BTAs in preventing SREs for metastatic cancers of solid tumours and to conduct local economic evaluation of Bisphosphonates and Denosumab.

Conclusions and results

Fair to good level of retrievable evidence:

Safety: Denosumab was associated with two time higher occurrence of hypocalcemia but with less renal toxicity compared with Zoledronic acid (ZA) but both had similar occurrence of osteonecrosis of the jaw (ONJ) event. No significant difference between12-weekly and 4-weekly regimens in adverse events for hypocalcemia and ONJ. However, less renal toxicity events found in 12-weekly ZA for breast cancer and prostate cancer compared to 4-weekly ZA.

Effectiveness:
BTAs (Denosumab and Bisphosphonates) significantly delayed time to first SREs, reduced the risk of first and subsequent SREs in all types of cancer except non-small cell lung cancer (NSCLC). Denosumab was superior in reducing risk of developing SREs followed by ZA and Pamidronate. Bisphosphonates significantly reduced the number of patients with SREs in patients with breast and prostate cancer only. There was a significant pain relief and better quality of life (QoL) in Bisphosphonates group compared to placebo group in breast and prostate cancer.

Between the different types of Bisphosphonates, ZA was the most effective in delaying the time to first SREs followed with Pamidronate and Ibandronate in breast cancer and lung cancer. However, in reducing risk of first and subsequent SREs, ZA significantly reduced in patients with breast cancer only while no difference in other types of cancers.

Pooled data from meta-analysis showed that Denosumab delayed the time to first SREs by 18% with Hazard ratio (HR): 0.82, 95% CI: 0.77, 0.87 for all types of cancer. Denosumab also significantly reduced the risk of first and subsequent SREs by 17% with rate ratio (RR): 0.83, 95% CI: 0.78, 0.88 for all types of cancer compared to ZA. Overall survival was similar for all types of cancer (HR: 0.94, 95% CI:

0.87, 1.01) except for lung cancer (HR: 0.79, 95% CI: 0.69, 0.89) where patients who received Denosumab significantly delayed by 21%. In terms of pain, Denosumab was favourable in reducing pain compared to ZA in breast cancer, prostate cancer and other solid tumours while Denosumab was found improve QoL in patients with breast cancer.

Comparison between the two different regimens (12-weekly and 4-weekly) showed that no difference in time to first SREs for ZA in breast cancer (HR: 1.06, 95% CI: 0.70, 1.60). Similar result for ZA in terms of risk of first and subsequent SREs (HR: 0.97, 95% CI: 0.83, 1.12) in breast cancer and prostate cancer. The evidence on the two different regimens of Denosumab was limited even though there was no significant difference for Denosumab in overall number of patients with SREs (Risk ratio: 1.96, 95% CI: 0.71, 5.38) due to the small sample size involved.

Ethical/social/organizational: One evidence in real-world practice showed that patients treated with Denosumab were more likely compliant compared to ZA. The number of percentage that switched agents was lower in the Denosumab group compared to ZA group within first, second and third year of administration. Thus, the higher levels of compliance and persistence may improve treatment effectiveness.

Economic: Based on the decision analytic model, the use of bone targeting agents in preventing SREs among Stage IV solid tumour patients with bone metastases is a cost-effective strategy. Within this evaluation, the most cost-effective option was 12-weekly intravenous ZA, yielding an ICER of RM 4,968.87 per QALY gained which is lower than the cost-effectiveness threshold of 1 GDP per capita. The estimated total financial implications for this strategy with 100% potential patients coverage was RM 8.8 million per year.

Recommendations (if any)

Based on this review, BTAs were found to be significantly delaying the development of SREs among metastatic cancers of solid tumours and hence, directly preserving quality of life and improve morbidity rate. This effect is particularly significant with ZA and Denosumab. Twelve-weekly IV ZA was found to be the most cost-effective option. Hence, it is the preferred choice in preventing SREs.

In general, BTAs were well tolerated with rare occasion of adverse events and is a recommended good clinical practice to initiate its' use soon after bone metastasis is diagnosed clinically. However, creatinine clearance must be closely monitored in patients receiving ZA in view of its potential side effect of renal impairment.

Methods

Systematic review of literatures

Studies were identified by searching the electronic database for published literatures pertaining to the use of BTAs in preventing SREs for metastatic cancers of solid tumours. The following databases were searched through the Ovid interface: MEDLINE, EBM Reviews-Cochrane Database of Systematic Reviews (2005 to April 18), EBM Reviews-Cochrane Central Register of Controlled Trials (March 2018), EBM Reviews-Health Technology Assessment (4th Quarter 2016), EBM Reviews-DARE, EBM Reviews-NHS Economic Evaluation Database (1st Quarter 2016) and Embase. Searches were also being conducted in PubMed, Horizon Scanning database, INAHTA database, and FDA database. Additional literatures were identified from the references of the retrieved articles. General search engine also be used to get additional web-based materials and information.

Decision analytic economic modelling

The economic evaluation was designed from provider perspective (Ministry of Health, Malaysia) based on mix-cased unit in general public hospital. The evaluation was conducted using literature-based Markov model (Excel) to compare the direct costs and quality adjusted life years (QALY) for hypothetical cohort of patients with primary solid tumour with bone metastases using the seven healths states in two disease conditions; stable and progressive within 3-month transition cycle and lifetime time horizon.

Further research/reviews required

Current evidence on the use of 12-weekly Denosumab was still limited, thus, further good quality research is warranted.

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