Reimbursement for bone loss prevention is different between women with breast cancer and men with prostate cancer: time for a revision

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Abstract

The hormone dependent breast and prostate cancers have in general a very good survival, due to the anti-hormonal treatment. A disadvantage of this treatment is the increased risk of osteoporosis and fractures. It is surprisingly to note that denosumab has the same impact on fracture reduction incidence for both sexes, but with different reimbursement criteria. Furthermore there is only reimbursement in case of osteoporosis and not for cancer patients who are at an increased risk of developing osteoporosis. The clinician detects the accelerated bone loss during follow-up, but has to wait until there is osteoporosis. The impact of osteoporosis on the quality of life is severe and underestimated. Management of cancer should not only focus on survival, therefore it is time to reconsider the reimbursement criteria, discuss the willingness of society to pay for bone health and make choices regarding the advice we give to our patients.

Key words: Breast cancer, denosumab, fractures, reimbursement, osteoporosis, prostate cancer, survival.

The two most frequent cancers in women and men in the industrialized world are breast and prostate cancers. For Belgium in 2012 there were 8288 men diagnosed with prostate cancer and 10,531 women with breast cancer (Belgium cancer Register, 2012). Their death rates are ranked as number 3 and 1 respectively, with a 5-years age-standardised relative survival of 85.5% and 93%, respectively (Table I) (Belgium Cancer Register 2011; Belgium Cancer Register 2012).

The figures show that treatment for both cancers have become very successful and have made these cancers a more or less chronic disease. Long-term anti-hormonal treatment is the keystone of this success. In postmenopausal women aromatase inhibitors (AIs) have emerged as the standard of care as adjuvant treatment in hormone receptor positive breast cancer (Gnant et al., 2015). The anti-hormonal treatment should be given for at least five years. Recent reports increasingly recommend extending the duration of 5 years (Blok et al., 2015). An extension in duration seems worthwhile but at present there are no data to support this for AIs. Men with prostate cancer receive androgen deprivation therapy and depending on the stage it can be given for several months to several years. A major side effect of these anti-hormonal treatments

Table I. — Incidence and mortality of breast and prostate cancer in Belgium.

| Tumor     | Breast | Prostate |
|-----------|--------|----------|
| Mean age* | 62     | 69       |
| Incidence** | 178.2  | 168.6    |
| Cri***    | 11.3   | 11.6     |
| Frequency | Nr 1: 35.3% | Nr 1: 27% |
| Death     | Nr 1: 20.2% | Nr 3: 9.3% |
| Mortality** | 42.8   | 27.0     |
| 5-years ASR survival**** | 85.5% | 93%       |

*Age, mean and years.
**Crude (all ages) rate (n/100,000 person years).
***Cri cumulative risk 0-74 years (%).
****ASR survival: Age-standardised relative survival.
for both cancers is accelerated bone loss (osteoporosis) and an increased fracture risk.

The morbidity and mortality of osteoporosis are severely underestimated in our society. The residual lifetime risk of fracture for women and men from age 60 is 44% (95% CI, 40-48) and 25% (95% CI, 19-31), respectively (Nguyen et al., 2007). For individuals with osteoporosis (BMD T-scores < or = -2.5), the mortality-adjusted lifetime risk of any fracture is 65% (95% CI, 58-73) for women and 42% (95% CI, 24-71) for men (Nguyen et al., 2007).

The incidence of osteoporosis and fractures in female breast cancer patients and prostate cancers patients is considerably increased compared to people with normal or osteoporotic bones. A recently published randomised, double-blinded controlled trial of denosumab vs. placebo in breast cancer patients revealed in the placebo arm of the trial a fracture rate after 3 years, 5 years and 7 years of respectively 10%, 16% and 27% (Gnant et al., 2015).

Treatment with bisphosphonates or denosumab significantly reduces the risk of fracture in postmenopausal women and men with osteoporosis. Randomised trials showed that both bisphosphonates as well as denosumab prevent AI induced bone loss in breast cancer patients (Coleman et al., 2012; Coleman et al., 2013b). Regarding the fracture prevention there are no studies, which directly compare a bisphosphonate with denosumab. The bisphosphonate studies in breast cancer patients, ZO-FAST and AZURE, show no difference in fracture rates (Coleman et al., 2013a; Coleman et al., 2014). A randomised controlled trial using adjuvant denosumab in breast cancer showed significantly reduced rate of clinical fractures (Gnant et al., 2015). Patients in the denosumab arm had compared with the placebo arm a reduction of 50% in the delayed time to first clinical fracture (hazard ratio 0.50 (95% CI 0.39-0.65), p < 0.0001) and a reduction in the total number of fractures by about half (Gnant et al., 2015). Denosumab has the same impact on the reduction of fracture incidence for hormone positive breast cancer as in prostate cancer treated with anti-hormonal therapy (Smith et al., 2009; Gnant et al., 2015). It is surprising therefore that the criteria for reimbursement of denosumab are different for women and men in Belgium (Table II) (RIZIV 5900200, 2013; RIZIV 5900100, 2015). There is no difference between women and men in reimbursement for denosumab if there is at least one bone metastasis of a solid tumour. In these cases the patient should receive 120 mg denosumab (Xgeva) every month (RIZIV 6160000, 2001).

Current guidelines recommend that breast cancer patients who receive an AI should be monitored for bone loss and intervention should be considered when bone mineral density decreases (Hadji et al., 2011). This approach does not only improve the quality of life but is also cost effective.

For adjuvant bisphosphonates on the other hand there is convincing evidence that disease-free and overall survival are improved in postmenopausal breast cancer patients (Gnant et al., 2012; Coleman et al., 2015). For denosumab there are no data regarding recurrence reduction and overall survival due to the small follow-up time of the ABCSG-18 for both cancers is accelerated bone loss (osteoporosis) and an increased fracture risk.

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Table II. — Criteria for reimbursement of denosumab (60 mg SC 1×/6 months) for a duration of 12 months.

| Should have the following conditions | Woman | Man |
|--------------------------------------|-------|-----|
| 1. Previous treated with oral bisphosphonate | Yes | Not applicable |
| or Contra-indication for oral bisphosphonate | Yes | Not applicable |
| 2. Postmenopausal | Yes | Not applicable |
| 3. Cancer | No | Yes |
| 4. Anti-hormonal treatment | No | Yes |

| And should also have at least one of the following conditions | | |
|---------------------------------------------------------------|---|---|
| Vertebral fracture | Yes | Yes |
| or T-score < -2.5 of the lumbar spine (L1-L4 or L2-L4) | Yes | Yes |
| or T-score < -2.5 of the hip | Yes | No |
| or T-score < -1.5 of the hip | No | Yes |
treatment. Long time management should include also attention for bone health. The willingness of society to pay for this approach can only be answered by the question: “How much are my bones worth when I’m alive?”.

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