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Opinion paper

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

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

	Woman	Man
Should have the following conditions		
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

trial. An update in the future could give use this information. At present there is also the D-CARE trial; this trial is on-going and uses a different doses of denosumab (ClinicalTrials.gov identifier NCT01077154, 2010). The D-CARE trial is the study of denosumab as adjuvant treatment for women with high-risk early breast cancer receiving neo-adjuvant or adjuvant therapy. Schedule of denosumab is the following: 120 mg SC once monthly for 6 months, 120 mg SC every 3 months for the next 4 and a half years. All patients should received oral calcium (at least 500 mg) and vitamin D (at least 400 IU) for 5 years. In total 4509 patients have been recruited for this trial. The study started in May 2010, the final data collection date for primary outcome is expected in October 2016 and the estimated study completion date is expected in October 2021. Nearly all men with prostate cancer will, despite androgen deprivation therapy, experience diseases progression; this is known as castration-resistant prostate cancer (CRPC). Recently a large RCT was published which showed that denosumab in men with CRPC significantly prolonged bone metastasis-free survival and delayed time to bone metastasis (Smith et al., 2012). In the early-disease setting for men with hormone refractory prostate cancer and women with breast cancer in the absence of circulating reproductive hormones, there is increasing evidence that changing the bone marrow environment appears to prevent metastatic disease at sites other than bone (Coleman et al., 2012).

When you look at significant benefits of adjuvant treatment in early stage breast cancer then there is an absolute difference in the disease free survival at 5 years for tamoxifen vs no tamoxifen: 14.2% (reduction of 39%), anastrozole vs. tamoxifen: 2.4% (reduction of 13%), letrozole vs. tamoxifen: 1.9% (reduction of 19%), trastuzumab vs. no trastuzumab: 6.4% (reduction of 24%) and zoledronic acid vs no zoledronic acid: 4.4% (reduction of 29%). Except the latter, all adjuvant treatments are reimbursed.

For women and men with osteoporosis there is a reimbursement for bisphosphonates and denosumab. For women and men with a hormone positive cancer who receive an anti-hormonal treatment (androgen deprivation therapy or AI, respectively), there is no reimbursement if they do not have osteoporosis. This is not appropriate because this group of patients is at a higher risk of developing fractures and a preventive approach would lead to the reduction of recurrences.

The most frequent cancers in women and men are becoming chronic diseases. Management of these diseases should not only focus on the treatment of the cancer but also on the side effects caused by the treatments. 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?".

References

Belgian Cancer Register 2012. http://www.kankerregister.org/Cijfers_over_kanker (consulted July 27, 2015).

Belgian Cancer Register: Cancer Incidence in Belgium 2008. Published in 2011. http://www.kankerregister.org/Statistieken_publicaties (Consulted July 27, 2015).

Belgian Cancer Register: Cancer Survival in Belgium. Belgium 2004-2008. Published in 2012.http://www.kankerregister.org/Statistieken_publicaties (Consulted July 27, 2015).

Blok EJ, Derks MG, van der Hoeven JJ, et al. Extended adjuvant endocrine therapy in hormone-receptor positive early breast cancer: current and future evidence. Cancer Treat Rev 2015;41(3):271-6.

Clinical Trials.gov identifier NCT01077154. Study of Denosumab as Adjuvant Treatment for Women With High Risk Early Breast Cancer Receiving Neoadjuvant or Adjuvant Therapy (D-CARE), 2010.https://clinicaltrials.gov/ct2/show/NCT01077154 (consulted July 27, 2015)

Coleman R, Gnant M, Morgan G, et al. Effects of bone-targeted agents on cancer progression and mortality. J Natl Cancer Inst 2012;104(14):1059-67.

Coleman R, de Boer R, Eidtmann H, et al. Zoledronic acid (zoledronate) for postmenopausal women with early breast cancer receiving adjuvant letrozole (ZO-FAST study):final 60-month results. Ann Oncol 2013a;24(2):398-405.

Coleman RE, Rathbone E, Brown JE. Management of cancer treatment-induced bone loss. Nat Rev Rheumatol 2013b; 9(6):365-74.

Coleman R, Cameron D, Dodwell D, et al. AZURE investigators. Adjuvant zoledronic acid in patients with early breast cancer: final efficacy analysis of the AZURE (BIG 01/04) randomized open-label phase 3 trial. Lancet Oncol 2014; 15(9):997-1006.

Coleman R, Powles T, Paterson A, et al. Adjuvant bisphosphonatetreatment in early breast cancer: meta-analyses of individual patient data from randomised trials. Lancet 2015 (in press).

Gnant M, Clézardin P. Direct and indirect anticancer activity of bisphosphonates: a brief review of published literature. Cancer Treat Rev 2012;38(5):407-15.

Gnant M, Pfeiler G, Dubsky PC, et al. Adjuvant denosumab in breast cancer (ABCSG-18): a multicentre, randomised, double-blind, placebo-controlled trial. Lancet 2015;S0140-6736(15)60995-3.

Hadji P, Aapro MS, Body JJ, et al. Management of aromatase inhibitor-associated bone loss in postmenopausal women with breast cancer: practical guidance for prevention and treatment. Ann Oncol 2011;22(12):2546-55.

Nguyen ND, Ahlborg HG, Center JR, et al. Residual lifetime risk of fractures in women and men. J Bone Miner Res 2007;22(6):781-8.

RIZIV 6160000, 2001. www.bcfi.be/PDF/RIZIV/6160000_FormDem_NL.pdf (consulted August 26, 2015).

RIZIV 5900200, 2013. www.bcfi.be/PDF/RIZIV/5900200_FormDem_NL.pdf (consulted August 26, 2015).

RIZIV 5900100, 2015. www.bcfi.be/PDF/RIZIV/5900100_FormDem_NL.pdf (consulted August 26, 2015).

Smith MR, Egerdie B, Hernández Toriz N, et al. Denosumab in men receiving androgen-deprivation therapy for prostate cancer. N Engl J Med 2009;361(8):745-55.

Smith MR, Saad F, Coleman R, et al. Denosumab and bone-metastasis-free survival in men with castration-resistant prostate cancer: results of a phase 3, randomised, placebo-controlled trial. Lancet 2012;379(9810):39-46.