GU radiation oncologists consensus on bone loss from androgen deprivation

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The majority of GU radiation oncologists in Canada attended a consensus meeting in November 2004. The topic of osteoporosis in men receiving androgen deprivation therapy (ADT) for prostate cancer was identified as a key theme. A chaired session with keynote speakers and review of the evidence took place followed by open debate. Participants were provided with background information.

Osteoporosis was defined as a T-score <= -2.5, but the importance of risk factors and clinical findings is noted. Dual DEXA is the current standard for assessment of bone density and relates well to fracture risk. The lifetime risk of fracture is 13% for men over the age of 50 years even without the influence of ADT. Lifestyle, dietary and supplementation advice are provided both to prevent and to manage osteoporosis. The role for prophylactic bisphosphonate therapy in men on ADT without osteoporosis has not been established. Follow-up DEXA scans are required to monitor density, risk and response to interventions. Fracture incidence and BMD should be considered in the trial design of studies involving prolonged ADT. Osteoporosis is a treatable condition and the oncologist should employ ADT with this knowledge. A follow-up e-mail survey was carried out regarding the consensus statement. Responses were received from 49 of the 69 attendees (71%), and overall there was an 89% agreement with the consensus statement. This is now adopted as national practice guidelines for radiation oncologists employed prolonged ADT in prostate cancer patients.

Key Words: castration, osteoporosis, fractures bone, consensus, prostatic neoplasms

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Introduction

The GU Radiation Oncologists of Canada (GUROC) are the unofficial body representing those who manage and treat genito-urinary cancers with radiation in Canada. Meetings have been held every 2 years since 2000.

The third GUROC meeting was held in Toronto,

November 12-13, 2004. All 98 radiation oncologists who practice GU oncology were invited, and 69 attended. The agenda had been developed by a steering committee with representation from across the country. One topic identified was that of osteoporosis in men undergoing androgen deprivation therapy (ADT) who have prostate cancer. There has been mounting evidence of accelerated bone density loss with the use of hormone therapy as well as concern that this is not generally being appreciated.[1] The intent was to develop a national consensus on the topic.

Background

Rates of bone loss and fracture risk

It is clear that bone density gradually decreases as men get older. The rate of bone loss is slow – up to 1% loss per year for the lumbar spine and 0·7% loss per year for the femoral neck.[3,4] It is established that bone density loss can accelerate with androgen deprivation therapy - with reported rates of up to 8% per year in the spine, and 4% per year in the femoral neck in the first 2 years then 1% per year thereafter. Data suggests that rates of bone loss are similar with medical or surgical castration.[5] Although bone loss is worsened, the major concern is with fractures and the related morbidity or even mortality.[6-9] In particular, Shahinian explored SEER-Medicare claims data on over 50,000 men and found nearly 20% of men on androgen deprivation therapy had a fracture at least 5 years after prostate cancer diagnosis compared with 12.6% not receiving androgen deprivation therapy.6 Smith took a random sample of 3887 men from Medicare claims data and found that the relative risk of any clinical fracture was 1.21 for those receiving LHRH versus not. Both studies show longer therapies increase the risk (especially for more than a year).[10]

Osteoporosis and fracture risk

For the purpose of consensus development and a review of evidence we have used a definition of osteoporosis as a bone mineral density (T score) value ≤ -2.5 standard deviations or less than the peak young adult male normal mean reference range.[11] It is known that the risk of hip fracture is 3 times higher for each standard deviation decrease in femoral neck bone mineral density. Other risk factors for future fractures include age over 75, prior atraumatic or low-trauma fracture (e.g. sustained in a fall from a standing height or less), frailty, a family history of osteoporosis, and low BMD.[11] Current evidence and expert consensus increasingly supports the view that these factors are likely also applicable in men.

Determining osteoporosis

The bone mineral density can be measured by dual energy x-ray absorptometry (DEXA scan), quantitative computed tomography or ultrasound. DEXA scan is the current standard. One should use the lowest T score of the total lumbar spine (L1-L4), total hip, or the femoral neck for diagnosing osteoporosis. To interpret changes over years on follow-up however one should use the change in g/cm^2. Use of the same DEXA machine improves accuracy and interpretation of results. The physician ordering the scan must be aware of the factors that can alter BMD, e.g. prior fracture, metastases, degenerative change, contrast agents, or rotation of the hip.

Prevention and management of osteoporosis

Many men with prostate cancer are already at risk for osteoporosis.[12] The lifetime risk of fracture is 13% for men over the age of 50 years even without the influence of ADT.[6,11] Smith estimates this risk at 6.51 per 100 person years increasing to 7.88 per 100 person years with LHRH therapy.[10] Lifestyle recommendations should include engaging in regular activity and a falls prevention program may be needed. Dietary advice (particularly adequate calcium, Vitamin D and protein, with low – moderate sodium and caffeine) should be provided, and patients should be advised to stop smoking and minimize or moderate alcohol consumption.[11,13] Supplemental vitamin D3 (400 – 800 IU/day) and supplemental elemental calcium (1200 – 1500 mg/day), should be encouraged.[2,11,14,15] The optimum doses of calcium and vitamin D are based on dietary recommendations. High calcium intake has been linked to a higher risk of developing prostate cancer. However this may be due to low vitamin D levels or other factors.[16]

Established osteoporosis should be treated with supplemental vitamin D, calcium and exercise in conjunction with bisphosphonate therapy.[11,17,18] There are, however, different potencies of bisphosphonates and provincial formularies may cover only certain preparations. Drugs other than bisphosphonates may be helpful (e.g. calcitonin, PTH, raloxifene), and may be a consideration in unusual cases. Although BMD is increased with the use of bisphosphonates, trials to definitively show that bisphosphonate therapy decreases fracture risk in men with osteoporosis receiving androgen ablation have not been performed. However for men with primary osteoporosis, bisphosphonates have been shown to reduce the incidence of vertebral fractures.[19]

The role for prophylactic bisphosphonate therapy in men on ADT without osteoporosis has not been

established.[17,20-22] In fact patients who have normal bone densities at presentation have a low risk of fracture. Large numbers of patients would need to be treated with bisphosphonates to see a population benefit - if at all. These medications may also have side effects and are not always tolerated.

Follow-up

The optimum frequency of repeat bone mineral density measurements has not been determined. The sensitivity of DEXA to changes in BMD needs to be considered as well as the baseline T scores, associated risk factors (especially steroid use) and if monitoring an intervention such as a bisphosphonate. Tests would therefore be done approximately every 1-3 years.[2] The same DEXA machine will yield much more comparable results.

Steps toward GUROC consensus

The GUROC session was chaired by Dr. Tom Pickles (BC Cancer Agency) who prepared draft consensus guidelines based on guidelines already in place in British Columbia.[2] Input was solicited from Dr. Graeme Duncan and Dr. Tom Corbett who prepared a draft document outlining the pertinent issues of theory, evidence and practice. At the GUROC meeting presentations were made by an osteoporosis expert, Dr. Angela Cheung (Endocrinology, Toronto Hospital) who gave further background information, and by Dr. Graeme Duncan who presented the BC guidelines based on data available up to that time (late 2004). After the presentations an open discussion followed, at which the draft consensus statement was discussed. There was insufficient time to agree on a consensus document at the meeting, and so it was decided to continue the process by means of email correspondence.

In February 2005 background documents, URL-links to established guidelines and a revised draft consensus statement were sent to all participants, along with a questionnaire regarding the statement. Responses were collated over the following 8 weeks. Overall the consensus statement received strong support. Details regarding the responses received appear at the conclusion of this article.

GUROC consensus statement

Osteoporosis and androgen deprivation therapy

Osteoporosis is a significant health concern in men over 65 years of age and is currently under-diagnosed and under-treated. Most men with prostate cancer are over 65 years of age. Androgen deprivation therapy (ADT) for prolonged periods is also a significant risk factor for inducing osteoporosis. ADT-induced osteoporosis is a potential source of morbidity and reduced quality of life. Fracture related complications may also carry an increased risk of mortality.

- A baseline DEXA scan assessing bone mineral density (BMD) should be performed if prolonged ADT is to be employed (defined as > 6 months, adjuvant or palliative). The physician who starts patients on prolonged ADT should discuss the possible development of osteoporosis with them.
- Adequate calcium and vitamin D intake, as well as moderate exercise/fall prevention is recommended for all men beginning ADT.
- Physicians commencing ADT should ensure that suitable arrangements for the monitoring of BMD and treatment are undertaken. For patients who have osteoporosis the oncologist should consider referral to an appropriate specialist or to the family physician.
- If BMD, history or plain films identify 'osteoporosis' (defined here as a T-score $\leq$ - 2.5) at any time, the patient should be considered for bisphosphonate therapy. Furthermore, these patients should be screened for secondary causes of osteoporosis (such as hyperthyroidism, hyperparathyroidism, malnutrition, rheumatic diseases, liver disease, alcoholism and drugs that affect bone metabolism) and steps to reduce fracture risk should be instituted.
- DEXA scans should be repeated on a regular basis (e.g. every 1-2 years) in patients who are undergoing ADT and have normal BMDs at baseline. More frequent follow-up DEXA scans may be considered in patients at higher risk e.g. osteoporosis/osteopenia at baseline, or other significant risk factors promoting osteoporosis (e.g. annually).
- Fracture incidence and BMD should be considered in the trial design of studies involving prolonged ADT.

Osteoporosis is a treatable condition and the oncologist should employ ADT with this knowledge. Prolonged androgen deprivation is an evidence-based intervention that improves overall survival in locally advanced or high-grade prostate cancer.

Consensus questionnaire response

By April 2005 we received responses from 49 of the 69 attendees (71%), and overall there was a

TABLE 1. **Summary of responses to consensus statement**

	Agree		Neutral		Disagree	
	n	%	n	%		%
There is a need for a consensus on this topic	46	94%	2	4%	1	2%
The draft recommendations in this report are clear.	45	92%	3	6%	1	2%
I agree with the draft recommendations as stated.	45	92%	1	2%	3	6%
The draft consensus report presents options that will be acceptable to patients.	43	90%	4	8%	1	2%
The draft recommendations are likely to be supported by a majority of my colleagues.	39	81%	6	13%	3	6%
This draft report should be approved as a consensus statement	44	90%	2	4%	3	6%
If this draft report were to be approved as a practice guideline, how likely would you be to use it in your own practice?	45	96%	0	0%	2	4%
Overall		**91%**		**5%**		**4%**

91% agreement with the consensus statement. Table 1 indicates the degree of acceptance of the consensus statement based on late 2004 information.

In January 2005 Shaninian's paper strongly supported the consensus.[6] At the time of submission of our consensus paper, Smith published further evidence of the increased fracture risk in this group of patients.[10]

Conclusion

With the approval, and subsequent publication of this national consensus document, the GUROC group hopes to prevent significant morbidity from the effects of androgen deprivation therapy. We plan to carry out an assessment of the implementation of the guidelines in due course. □

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