Research paper

Assessment of bone health in breast cancer patients starting adjuvant aromatase inhibitors: A quality improvement clinical audit

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ABSTRACT

Introduction: Adjuvant Aromatase Inhibitors (AIs) predispose breast cancer patients to accelerated bone loss. Guidelines recommend initial screening and follow up of bone mineral density with dual energy X-ray absorptiometry (DEXA) scan. In this audit we assessed the rate of adherence to these guidelines and introduced awareness measures to improve it.

Methods: All post-menopausal women who started upfront adjuvant AIs (letrozole in all patients) between January 2007 and December 2013 were retrospectively identified. The standard to be audited was "These patients should have a baseline DEXA scan requested within the first 3 months of starting adjuvant AIs therapy". A 90% or more compliance was accepted as satisfactory. Corrective measures in the form of educational and awareness sessions followed by re-auditing of the practice over the subsequent 12 months were planned in case of lower compliance rate.

Results: Three hundred and sixty seven eligible patients were identified. Baseline DEXA scan was performed in 188 (51.2%) patients. As planned, this result triggered the conduction of 4 consecutive educational sessions over a period of 2 weeks. Re-auditing the practice in the pre-defined subsequent subjects showed compliance in 47/52 (90.4%) patients.

Conclusion: This study of a sizable cohort confirms previous observations that adherence to skeletal health guidelines in this patient population is less than adequate. Adherence is improved dramatically by raising the awareness of relevant physicians.

1. Introduction

Breast cancer (BC) is the most frequently diagnosed cancer and the leading cause of cancer related death among women worldwide [1]. The incidence of BC is increasing in many regions of the world [2].

Surgical resection is the main curative treatment of early BC. In patients with oestrogen receptor positive (ER+) tumors, the outcome can be improved by depriving microscopic disease from oestrogen. Tamoxifen, a selective ER inhibitor improves recurrence free survival (RFS) and reduces breast cancer mortality in these patients [3]. Multiple randomized clinical trials confirmed the superiority of adjuvant aromatase inhibitors (AIs) when compared

with tamoxifen in post-menopausal women [4]. Thus AIs (letrozole, anastrazole and exemestane) have become the standard adjuvant hormonal treatment in post-menopausal women with ER+ BC. AIs profoundly reduce the levels of circulating oestrogen, subsequently having deleterious effects on skeletal health. Prolonged treatment with AIs increases bone resorption, reduces bone mineral density (BMD) and increases the risk of fracture [5].

Guidelines and consensus guidance statements highly recommend assessment of skeletal health of these patients including performing a Dual Energy X-ray absorptiometry (DEXA) scan and subsequent Life style and medicinal intervention guided by T score results [6–8]. Consequently, oncologists assumed the unusual role of screening and management of cancer treatment induced bone loss. Whether these guidelines are implemented in real life daily practice remains largely an unanswered question. In an attempt to answer this question, we conducted a large audit to identify if a baseline DEXA scan was requested at the time of starting adjuvant

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AIs. In addition, we introduced correctives measures and subsequent re-auditing of practice.

2. Patients and methods

All patients (n=554) who started any adjuvant hormonal therapy for newly diagnosed ER+ early BC between January 2007 and December 2013 at King Faisal Specialist Hospital & Research Centre (Jeddah) were identified from pharmacy database. Electronic and paper medical records of these patients were screened. During the above and the subsequent audit periods, the number of oncologists treating patients with BC increased from 3 (1 consultant and 2 assistant consultants) to 6 (3 consultants and 3 assistant consultants). All consultants received oncology higher medical training and certification in North America, Canada or Europe while all assistant consultants were trained in Middle Eastern countries. Three hundred and sixty seven out of 554 patients were post-menopausal and started upfront adjuvant AIs (letrozole in all patients) and were the subject of the primary audit. The standard to be audited was "These patients should have a baseline DEXA scan requested within the first 3 months of starting adjuvant AIs therapy". This information was extracted from the electronic medical records. Investigators extracted and analyzed the data over a period of 3 months (July-September 2014). A 90% or more compliance with the standard was accepted as satisfactory. Corrective measures followed by re-auditing were planned if lower compliance rate was achieved. Corrective measures comprised of 4 consecutive educational sessions over a period of 2 weeks (December 2014) targeting junior and senior oncologists. The sessions addressed the rational of assessment and management of skeletal health in these patients and attempted to raise the awareness to guidelines. These sessions were in the form power point presentations delivered by the audit lead (the first author of this manuscript). Contents of awareness sessions included (a) Effects of AIs on oestrogen synthesis. (b) Bone health analysis of large adjuvant trials confirming detrimental effect of AIs on BMD. (c) Local hospital guidelines. (d) International guidelines and consensus guidance statements including (not limited to) NICE, ASCO, St Gallen and ESMO guidelines. (e) Clinical risk factors for fracture. (f) Recommendations of above guidelines: "A baseline DEXA scan is an integral tool for assessing skeletal health of patients starting adjuvant AIs for the treatment of ER+ BC and to offer calcium, vitamin D and bone modifying agents if T score < −2″. (g) Rationale of using bone modifying agents (bisphosphonates and denosumab) in the prevention of AIs induced bone loss. In particular, oncologists were encouraged to request a base line DEXA scan for new patients at the time of starting adjuvant AIs. Compliance with the standard was planned to be re-audited for all eligible patients who will receive letrozole during the subsequent 12 months (January December 2015).

3. Results

3.1. Compliance with the standard

All patients were under follow up for > 6 months from date of starting adjuvant AIs. Baseline DEXA scan was requested and performed in 188/367 (51.2%) patients within 3 months of starting treatment. This compliance rate is considered below the pre-defined target of 90% and thus corrective measures (as detailed in methods section) were undertaken. Noncompliance with the audit standard was seen in 179 (48.8%) patients of whom only 35 patients had a later (range: 4–49 months) DEXA scan assessment and there was no evidence of such assessment in the remaining 144 patients.

These results were disseminated to all members of the oncology team during one of the regular departmental quality meetings.

3.2. Re-audit

Fifty two patients started upfront adjuvant AIs for newly diagnosed ER+ early BC between January 2015 and December 2015. Baseline DEXA scan was requested and performed in 47/52 (90.4%) patients. These results were disseminated to all oncologists. Relevant treating oncologists were notified of their individual patients (number=5 patients) who did not undergo a baseline DEXA scan during the re-audit period.

4. Discussion

Recommendations of international guidelines consistently recommend assessment of skeletal health of women with ER+ BC receiving adjuvant AIs including the performance of a baseline DEXA scan [7-12]. The United Kingdom (UK) National Institute of Clinical Excellence (NICE) appraises medical interventions and publishes quality standards designed to drive improvements within particular areas of health or care. In addition, NICE considers the cost of these interventions to reassure commissioners that the services they are purchasing are also cost effective. NICE guideline clearly recommend performing a baseline DEXA scan to assess BMD for women with early BC starting adjuvant AIs [6]. In line with the above, our local guidelines recommend a baseline DEXA scan for these patients and to offer calcium, vitamin D and bisphosphonates if T score < −2.

Clinical audit is a quality improvement cycle that involves measurement of the effectiveness of health care against agreed and proven standards for high quality and taking action to bring practice in line with these standards so as to improve the quality of care and health outcomes (Fig. 1).

Based on these principles we designed an audit to identify if a baseline DEXA scan was requested at the time of starting adjuvant AIs in post-menopausal women with ER+ BC. The results of our audit show that about half (48.8%) of eligible patients were not screened according to guidelines. Consequently, some unscreened patients will miss the opportunity to receive specific bone directed preventative and therapeutic treatment when indicated. To our knowledge, there are only 3 previous reports in the literature
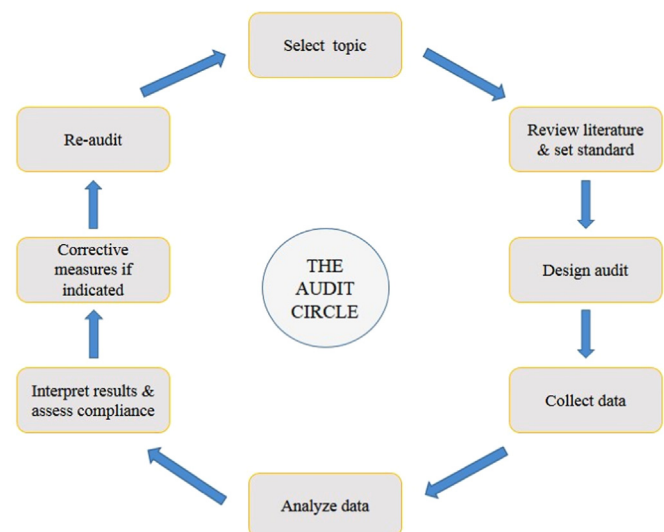

Fig. 1. Principles of the clinical audit circle.

investigating the compliance to guidelines and all confirm low levels (38%, 40.7% and 54%) of adherence [13–15].

The reasons for low adherence are not clear. Possible reasons include: (a) Oncologists may consider bone health a trivial issue in the context of cancer diagnosis and thus focus on anti-cancer treatments and follow up to detect recurrence ignoring bone health. (b) Oncologists may assume that screening for osteoporosis in these postmenopausal women will be addressed by the general practitioner or family doctor regardless of the use of AIs. (c) Oncologists' historical scope of work centres on the use of anti-cancer treatments and managing their acute side effects and therefore long-term bone health issues may seem non-relevant to the speciality.

We proposed that these 3 possible reasons are likely to arise from lack of awareness. Therefore, we planned and then conducted educational sessions targeting junior and senior oncologists to raise the awareness and encourage compliance with the guidelines (as detailed in Methods section).

Our work is the largest to be reported with 367 patients assessed in the first part of the audit compared to 42, 54 and 292 patients in other reports. Methods and results of these report are summarized in table 1 [13–15]. One of these was only reported in an abstract form [15]. Only our study and that conducted in the UK adopted a structured clinical audit design with initial auditing, introduction of corrective measure and subsequent re-auditing to complete the audit circle (Fig. 1). The UK audit selected a random convenience sample of 100 patients with a new diagnosis of BC diagnosed between April 2012 and April 2013. Only 42 of these patients were post-menopausal and started adjuvant AIs. Only 38% (16/42) of these patients received DEXA scans. They disseminated the results to the breast multidisciplinary team and conducted relevant educational and awareness activities. This was followed by re-auditing the practice on monthly basis; January (n=10), February (n=13) and March (n=11) achieving a collective compliance rate of 32/34 (94.1%) [13]. In contrast, we assessed the practice in much larger unselected population (n=367) representing all eligible patients treated over 7 years. After introduction of corrective measure, we re-audited a larger number of patients (n=52) over a longer period of practice of 12 months (Table 1). Despite these differences, both complete audits followed the same structured design and concluded similar results which are: (a) Compliance to guidelines is less than satisfactory. (b) Compliance is improved by education and raising the awareness to guidelines.

DEXA scan is the gold standard for assessing bone mass in clinical practice. It measures BMD at the spine and hip. Results can be interpreted using the World Health Organization T score. This information is used to diagnose osteopenia and osteoporosis and can predict individual's risk of fracture and thus guiding physicians to advise patients about the use of appropriate treatments [16]. For these reasons, all guidelines recommend a baseline DEXA scan for all post-menopausal women starting adjuvant AIs for ER+ early BC. Such assessment will define those patients with low BMD and consequently at risk of developing bone fractures.

Some guidelines (for example, American Society of Clinical Oncology [ASCO] and National Comprehensive Cancer Network [NCCN] guidelines) recommend initial assessment and thresholds for bone-directed therapy based primarily on BMD. Other guidelines include clinical risk factors for assessment and treatment decisions. An international expert panel recommend treatment of all patients with T score ≤ -2.0 and those with at least two of the following risk factors: T-score < -1.5, age > 65 years, body mass index < 20 kg m^2, family history of hip fracture, personal history of fragility fracture after 50 years of age, oral corticosteroid therapy > 6 months and cigarette smoking [17]. Additionally, the panel recommend considering baseline biochemical assessment including serum calcium, parathyroid hormone and 25-OH-Vitamin D Levels, and markers of bone turnover [17].

The World Health Organization fracture risk assessment tool (FRAX) has been developed to evaluate fracture risk in general population. It is based on individual patient models that integrate the risks associated with clinical risk factors as well as BMD at the femoral neck. The FRAX models have been developed from studying population based cohorts from Europe, North America, Asia and Australia. The most recent version (FRAX V3.10) was released in March 2016. Currently available versions have models suitable for population from 58 countries (not including Saudi Arabia). In its complete form, the FRAX tool is a computer driven system in which 12 patient's characteristics are entered. These characteristics are age, gender, weight, height, previous fracture, current smoking, use of glucocorticoids, rheumatoid arthritis, secondary osteoporosis, alcohol consumption of ≥ 3 units/day and femoral neck BMD.

The use of FRAX is expected to identify those patients at risk of bone fracture whom otherwise are not identified solely by BMD assessment. However, some experts addressed its limitations in term of accuracy, applicability and practicality. Lewiecki et al., explained that sometime FRAX results in values for 10-year probability of fracture that are counterintuitive and inconsistent with some of the treatment recommendations. Not all risk factors are straightforward. Previous fractures are not clearly defined, and could include fracture sites not related to osteoporosis, such as fingers and toes. Additionally, some patients with arthritis declare they have rheumatoid arthritis, although in fact it may be another form of arthritis. According to the FRAX model, it is possible for patients with normal T-scores (-1.0 or better) to be identified as candidates for treatment even though drugs approved for treatment of osteoporosis have not been shown to reduce fracture risk in patients with T scores better than -1.5. FRAX considers only femoral neck T score, yet some patients may be at high risk of fracture with a low lumbar spine T score despite a relatively good femoral neck T score [18].

Despite the above limitations clinical risk factors/FRAX remain valuable tools in addition to BMD measurement by DEXA scan in post-menopausal women starting adjuvant AIs.

Measures to maintain skeletal health and to reverse the process of bone loss are available. These include changes in life style, dietary advice, calcium and vitamin D supplements and bone modifying agents such as bisphosphonates and denosumab [19–22]. Bisphosphonates, in particular Zoledronic acid has been shown to have an additional *anti*-tumour effect [23]. They reduce the rate of recurrence in the bone and improve breast cancer

Table 1
Methods and results of reports in the literature auditing the compliance to guidelines.

	Dong H et al.	Gibson K et al.	Kamboj S et al.	Our audit
Reference	[13]	[14]	[15]	
Type of report	Publication	Publication	Abstract	Publication
Setting	1 hospital	1 hospital	2 hospitals	1 hospital
Number of eligible patients	42	54	292	367
Compliance with standard	38%	40.7%	54%	51.2%
Corrective measures	Yes (education and awareness)	No	No	Yes (education and awareness)
Re-auditing	Yes	No	No	Yes
Number of patients	34			52
Compliance	94.1%			90.4%

survival in post-menopausal women with BC [24,25]. Recently, denosumab was reported to improve RFS when compared with placebo in an updated analysis of the ABCSG-18 trial indicating a probable anti-tumour effect [26]. Detailed discussion of these interventions is beyond the scope of this report.

5. Conclusion

This study of the largest reported cohort confirms limited previous observations that adherence to skeletal health guidelines in this patient population is less than adequate. Hospitals and health institutions managing these patients should consider assessing and addressing this issue. Adherence is dramatically improved simply by raising the awareness of relevant physicians.

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