DOWNLOAD PDF THE USE OF BISPHOSPHONATES IN THE MANAGEMENT OF ADVANCED BREAST CANCER A.H.G. PATERSON

Chapter 1 : Palliative care consultations in advanced breast cancer (eBook,) [calendrierdelascience.com]

This chapter discusses the evidence of the usage of biphosphonates in the palliative care setting. Biphosphonates were used in malignant bone disease during the s, which then resulted in an advance in the management of patients with bone metastases.

Advanced Search Abstract Breast cancer is the leading type of cancer among women, and bone metastases are common in patients with breast cancer, affecting more than half of all patients with advanced disease. Bisphosphonates are the current standard of care for preventing skeletal complications associated with bone metastases. Clinical trials investigating the benefit of bisphosphonate therapy have used a composite end point defined as a skeletal-related event SRE or bone event, which typically includes pathologic fracture, spinal cord compression, radiation or surgery to bone, and hypercalcaemia of malignancy. Bisphosphonates significantly reduced the incidence of these events. Zoledronic acid, pamidronate, clodronate and ibandronate have demonstrated efficacy compared with placebo. Zoledronic acid has also been compared with another active bisphosphonate i. Bisphosphonates effectively reduce and prevent skeletal complications in patients with bone metastases from breast cancer. Preclinical data suggest that bisphosphonates have antitumour effects. Bisphosphonates may also be of use in the adjuvant setting. Median survival for women with breast cancer is approximately 2 years after an initial diagnosis of bone metastases [1]. These patients, therefore, are at long-term risk for developing skeletal complications from bone metastases [6]. These skeletal complications include severe bone pain that may require strong narcotics or palliative radiation therapy, pathologic fracture, spinal cord or nerve root compression, and hypercalcaemia of malignancy HCM. The resulting skeletal morbidity can substantially reduce quality of life [7]. Across all tumour types, patients with breast cancer have the highest incidence of skeletal complications [8 â€” 11]. These complications are the result of increased bone resorption that is characteristic of the bone lesions associated with malignant breast cancer. Therefore, therapies that effectively inhibit bone resorption can be expected to reduce the risk of skeletal complications. Bisphosphonates for the treatment of bone metastases Bisphosphonates have emerged in recent years as a highly effective therapeutic option for the prevention of skeletal complications secondary to bone metastases. Bisphosphonates bind preferentially to bone at sites of active bone metabolism and are released from the bone matrix during bone resorption. They are taken up by osteoclasts and potently inhibit osteoclast activity and survival, thereby reducing osteoclast-mediated bone resorption [12]. Newer nitrogen-containing bisphosphonates, such as zoledronic acid, pamidronate, and ibandronate, have a unique mechanism of action and increased clinical activity compared with first-generation bisphosphonates, such as etidronate and clodronate [13]. In particular, the nitrogen-containing bisphosphonates inhibit the mevalonate pathway of cholesterol biosynthesis in vitro and prevent protein prenylation in osteoclasts in vivo [13]. The post-translation modification or prenylation of small guanosine triphosphate-binding proteins, such as Ras, Rho and Rac, require two isoprenoid lipid intermediates: Prevention of prenylation occurs when the enzyme farnesyl diphosphate synthase is inhibited, thus limiting production of farnesyl diphosphate and geranylgeranyl diphosphate, which then inhibits osteoclast activity [13]. The nitrogen-containing bisphosphonates are more potent than first-generation compounds by several orders of magnitude and consequently can be safely administered via relatively short intravenous i. The clinical benefits of bisphosphonate therapy have been evaluated in a large number of clinical trials designed to capture data on skeletal complications Table 1 [8 , 14 â€” 23]. The majority of these trials have used a composite end point defined as a skeletal-related event SRE or bone event, which includes pathologic fracture, radiation therapy for bone pain or to treat or prevent a fracture, surgery to stabilize bone fractures, spinal cord compression and HCM. Such composite end points capture data on all clinically relevant events and are more likely to detect therapeutic benefits when treatment effects and disease morbidity are multifaceted [24]. Using a composite definition of skeletal events, it is possible to assess treatment effect using a variety of outcome analyses.

However, first-event analyses capture information only about the first event and ignore data on all subsequent events that occur in any given patient. Skeletal morbidity rates or skeletal morbidity period rates SMPR assess the total number of events that occur during a designated time period i. These analyses account for the occurrence of multiple skeletal events but assume that these events occur at a constant rate. However, clinical evidence suggests that patients with bone metastases exhibit considerable variation in both the number of skeletal events they experience and the rate at which these events occur [26]. Moreover, skeletal events do not demonstrate random distribution but often occur in clusters. Therefore, analyses that assume a linear event rate or random distribution e. Poisson regression analysis may overestimate treatment effects [27]. In contrast, multiple analyses account for non-constant event rates and are able to model all events and the time between events. Therefore, multiple event analyses are able to account for inter- and intrapatient variations in event rates and provide a statistically robust and comprehensive assessment of skeletal morbidity throughout the entire length of follow-up [28]. Andersen-Gill multiple event analysis calculates a hazard ratio that indicates the risk of skeletal events between two treatment groups. Recently, non-parametric methods for multiple event analysis have also been described by Ghosh and Lin [29] and by Cook and Lawless [30]. These models calculate the cumulative incidence of skeletal complications and allow for right-censored data, thus accounting for death or study discontinuation for other reasons. Collectively, both first-event and multiple-event statistical analyses provide sensitive and comprehensive assessments of the clinical benefit of bisphosphonates in patients with bone metastases. Bisphosphonates approved for the treatment of bone metastases from breast cancer Several bisphosphonates both oral and i. The more potent nitrogen-containing bisphosphonates are administered i. This study assessed the number of HCM episodes, courses of radiotherapy to bone, and pathologic fractures expressed as events per patient-years. After a median follow-up of approximately 14 months, there was no statistical difference between treatment groups in the percentage of patients with either HCM, radiotherapy to bone, or fractures. However, the statistical methodology used in this trial has been criticised because of the potential for overestimation of treatment effects [34]. This is a particular concern given that the majority of patients died before they completed the month study. Time to first SRE was later updated by Pavlakis and Stockler [33] based on an analysis of patients. In the updated analysis, time to first bone event was significantly delayed 9. Two other placebo-controlled trials of oral clodronate have also been published. In the study by Kristensen et al. There was no effect of clodronate on progression of bone disease or survival. Most recently, Tubiana-Hulin et al. In this study, bone events were defined as HCM, radiotherapy to bone, pathologic fractures including spinal cord compression , increase or onset of bone pain, or death due to bone metastases. These studies demonstrated that clodronate significantly reduces and delays skeletal morbidity in patients with bone metastases. Intravenous pamidronate The efficacy and safety of i. These trials each individually showed that pamidronate significantly reduced the incidence and delayed the onset of SREsâ€”defined as pathologic fractures, spinal cord compression, surgery to treat or prevent fractures, HCM, and need for radiation to boneâ€—compared with placebo [17 , 18]. In the study reported by Hortobagyi et al. Likewise, in the study reported by Theriault et al. Given these results, which are based on conservative clinical end points, i. These results were later confirmed in a study reported by Hultborn et al. Skeletal-related events were not assessed in this study. Intravenous zoledronic acid Zoledronic acid has been compared directly with pamidronate and was shown by multiple-event analysis to be significantly more effective at reducing the risk of SREs among breast cancer patients Table 4 [35 â€” 37]. More recently, zoledronic acid 4 mg via 15 min infusion every 4 weeks for 1 year has been compared with placebo in Japanese women with bone metastases from breast cancer Table 5 [23]. Similar to the pamidronate trials, patients enrolled in this trial had predominantly osteolytic lesions. Zoledronic acid also consistently reduced Brief Pain Inventory scores from baseline in this study. At every time point, patients in the placebo group had either no change or an increase from baseline in their median pain score, whereas patients in the zoledronic acid group had a decrease from baseline in their median pain score at every time point. Intravenous and oral ibandronate Most recently, ibandronate both oral and i. A randomised, placebo-controlled trial of 2 or 6 mg i.

The primary efficacy end point was the SMPR, defined as the number of week periods on study in which a patient experienced a new bone event divided by the number of periods on study. Bone events were defined as pathologic fracture, radiotherapy to treat bone pain or impending fracture, or surgery for bone complications. Ibandronate 2 mg demonstrated no significant clinical benefit. Based on these placebo-controlled trials, both oral and i. Summary of clinical trials Efficacy In patients with advanced breast cancer and bone metastases, the administration of oral or i. Safety of intravenous and oral bisphosphonates In general, bisphosphonates are well tolerated. As a class, i. Intravenous bisphosphonates can also have adverse effects on renal function. These effects are dependent on the dose and infusion rate, but are generally mild to moderate in severity i. The incidence of severe renal adverse events is generally low. Effects on pain Several bisphosphonate trials have reported statistically significant improvements in pain compared with placebo [33], and bisphosphonates reduce the need for radiotherapy to bone, which serves as a surrogate for bone pain. In a systematic review of 25 randomised trials in metastatic breast cancer in which pain was evaluated, bisphosphonates generally had a beneficial effect [41]. The recent trial of zoledronic acid in Japanese women provides the most comprehensive evaluation of change from baseline score across time using the Brief Pain Inventory. Zoledronic acid consistently reduced bone pain from baseline at every monthly evaluation throughout the month study [23]. Currently, however, there is insufficient evidence to recommend bisphosphonates as first-line therapy for the treatment of bone pain [42], and the American Society of Clinical Oncology guidelines recommend that the current standard of care for cancer pain should not be displaced by bisphosphonates [43]. Current data suggest that bisphosphonates can result in improvements in QoL or reduce declines in QoL in patients with metastatic breast cancer [41]. For example, a significant improvement in QoL was demonstrated for patients treated with 6 mg ibandronate for 96 weeks compared with placebo [44]. In a study by Weinfurt et al. Collectively, these studies suggest that bisphosphonate therapy may have previously unappreciated benefits in terms of improved QoL during the course of treatment. Effects on biochemical markers of bone metabolism Bisphosphonates have profound effects on bone cell function that can be monitored using specific biochemical markers. In particular, markers of type 1 collagen breakdown have been evaluated in an attempt to both predict clinical outcome and identify a surrogate marker for individual patient benefit. Early small studies suggested a link between bone resorption rates and both pain relief [46] and the risk of fracture [47] during treatment with pamidronate. More recently, evidence from the large phase III trials of zoledronic acid has confirmed the relationship between bone resorption as measured by urinary NTX and skeletal morbidity, disease progression and death across a broad range of tumours affecting bone both with [49] and without [50] concomitant bisphosphonate treatment. The potential use of biochemical markers to refine the selection of patients for bisphosphonate treatments, and optimise both the schedule of administration and cost-effectiveness of bisphosphonate therapy is a current area of active research. Antitumour effects of bisphosphonates The activity of bisphosphonates in preventing bone metastases is an area of active investigation [51]. Preclinical studies suggest that bisphosphonates have direct antitumour effects in vitro and can reduce skeletal tumour burden and prevent the development of bone metastases in animal models [46]. Bisphosphonates have also demonstrated synergistic antitumour effects in combination with chemotherapy in breast cancer models [52]. Several clinical trials of oral clodronate and i. Long-term follow-up data from three trials of oral clodronate were recently reported. Of these, the most compelling data were those reported by Powles et al.

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Open in a separate window More recently, the AZURE trial was a randomized open label trial of standard therapy versus standard therapy and zoledronic acid given for five years in women with stage II or III breast cancer. However in a planned subgroup analysis, zoledronic acid improved DFS in women who were more than 5 years since menopause at trial entry [23]. Again DFS did not differ between groups at a median of There was no benefit seen for overall survival between the two treatment arms although there was a numerical difference in deaths in women over 50 years of age, favoring the clodronate arm [22]. Given these and other conflicting results, an individual patient data meta-analysis was undertaken, with the results being presented at the San Antonio Breast Cancer Symposium, [13]. This analysis included 36 trials comprising patients, with primary outcomes of time to recurrence TTR , time to first distant recurrence TFDR and breast cancer mortality. Among all women the results showed no improvements in recurrence rate Among the 11, post-menopausal women included in this analysis, significant improvements were seen in rates of distant recurrence Ten-year breast cancer mortality was also significantly improved in post-menopausal women in the bisphosphonate arm with mortality rates of The effect was seen irrespective of bisphosphonate type. There were no effects in pre-menopausal women in particular, no deleterious effects and no effects on non-breast cancer deaths, contralateral breast cancer or local-regional recurrence. In summary, this EBCCTG overview demonstrated a positive effect from bisphosphonates in a pre-determined sub-group analysis, resulting from consistent findings from multiple well-conducted trials. The finding is plausible, and the results support a modified vicious cycle hypothesis [26,27]. The exact mechanism of an enhanced anti-tumor effect of bisphosphonates in a low estrogen environment is uncertain, but certainly feasible [2,28,29]. One hypothesis may be that, by preventing enhanced bone destruction induced by the lack of estrogen, bisphosphonates interfere with the tumor-growth-supportive functions of bone-derived growth factors demonstrated in the vicious cycle hypothesis [26,28]. Alternately, low estrogen levels may not be the cause, other possibilities include increased levels of pro-inflammatory proteins leading to enhanced macrophage activity in the aging process reduced by bisphosphonates [30]. The magnitude of benefit of bisphosphonates is similar, if not greater than, other strategies that have been widely adopted in the breast cancer clinic. The absolute benefit in mortality for post menopausal women of 3. Further discussion presented included a rational approach as to whom to offer bisphosphonate therapy to. Suggested populations included; patients with osteopenia or osteoporosis, patients on aromatase inhibitors in whom the administration of bisphosphonates may ameliorate the accelerated loss of bone mineral density seen with aromatase inhibitors [33â€”35] , those with higher risk disease by stage, grade and receptor status. The question of which bisphosphonate to use may be answered with the results of the SWOG trial, that will likely be presented in [36]. Interim toxicity and patient preference results of SWOG suggest clodronate may be the preferred bisphosphonate. After 3 years of therapy, rates of osteonecrosis of the jaw were lowest for clodronate 0. Adjuvant bisphosphonates DO NOT represent a gold-standard for post-menopausal women with higher risk breast cancer 3. The first point to consider is whether or not a meta-analysis of subgroups should be used to influence clinical decision making? Subgroup analysis have an increased probability of type I error false positive when the null hypothesis is true negative trial. This leads to difficulty in interpretation. Hypotheses tested usually address an overall treatment effect in the study population, with no assumption of homogeneity of effect across subgroups. The direction, not magnitude, of the treatment effect is expected to be the same in subgroups. Stratification or regression techniques can be used to adjust the overall comparison for subgroups or covariates. However, subgroup analyses are generally of secondary interest and more appropriate for hypothesis generation for future studies. If data from the EBCTCG meta analysis will be used to change clinical practice, this will be the first time that

predominantly unstratified subgroup analysis has been used for decision making. This is methodologically concerning as a precedence as there is a higher than desirable chance the findings are a false positive. In addition to the validity of a sub group analysis changing clinical practice, the issue of patient selection was discussed. Do all post-menopausal women benefit from adjuvant bisphosphonates or can we identify a subgroup more likely to benefit? If adjuvant bisphosphonates predominantly reduce bone metastases; are patients with higher bone turn-over more likely to develop bone metastases? Therefore would adjuvant bisphosphonates predominantly be active in patients with higher bone turn-over? For example, if we use the use of an adjuvant aromatase inhibitor as a surrogate for high turnover [21,22,38â€”43] it appears that there is indeed greater benefit in this patient population Fig.

Chapter 3 : - NLM Catalog Result

Bisphosphonates have played an important role in the treatment of breast cancer, mainly in patients with bone metastasis, by reducing the risk of fracture, spinal cord compression, and hypercalcemia. Both oral and intravenous products are available and have strong supporting clinical evidence.

Chapter 4 : Use of bisphosphonates in the management of advanced breast cancer - Oxford Scholarship

The use of bisphosphonates in the treatment of bone metastases from breast cancer improves palliation of potential symptoms. A benefit from adjuvant use is being studied. Background: Bone is the most frequent site of metastasis in patients with breast cancer.

Chapter 5 : The Role of Bisphosphonates in Early Breast Cancer

Abstract. Clinical trials are investigating the use of bisphosphonates in patients with early (nonmetastatic) breast cancer. Results from trials of clodronate are generally encouraging but somewhat contradictory.

Chapter 6 : Bisphosphonates in breast cancer | Annals of Oncology | Oxford Academic

Randomised trials in advanced breast cancer have shown that one of these major events occurs, on average, every months [1, 2]. The average life expectancy from diagnosis of bone metastases is 2 years, with up to 20% of patients surviving 5 years.