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Effects of zoledronic acid on metastatic bone pain in cancer of the prostate: A randomised controlled trial

MO Akinwale[1], OA Soyannwo[2], OO Aikomo[2], AT Orunmuyi[3], B Kolude[4] and EO Olapade-Olaopa[5]

Department of Anaesthesia[1], College of Medicine, University of Ibadan,
Department of Hospice and Palliative Care[2], University College Hospital, Ibadan
Departments of Radiotherapy/Nuclear Medicine Centre[3], Oral Pathology[4] and Surgery[6],
Urological Section, College of Medicine,
University of Ibadan, Ibadan, Nigeria

Abstract

Background: Advanced cancer of the prostate often causes pain that can be severe requiring palliation with analgesics. Zoledronic acid, a third-generation bisphosphonate, has not been primarily used as an adjunct to treat pain in patients with metastatic bone secondary to advanced prostate cancer in Nigeria. The study investigated the effects of 3 doses of Zoledronic acid, at 4-weekly intervals, in addition to the analgesic regimen of oral morphine, diclofenac, paracetamol and amitriptyline, on bone pain in patients with metastatic prostate cancer .

Methods: A prospective randomized open-labelled trial in which forty patients with moderate to severe bone pain due to metastatic prostate cancer were recruited after institutional ethics approval. Patients were assigned to two groups: The Control (C) group received liquid oral morphine, diclofenac, paracetamol and amitriptyline. Zoledronic acid (ZG) group received 3 doses of Zoledronic acid at 4-weekly intervals in addition to liquid morphine, diclofenac, paracetamol and amitriptyline. Severity of pain and quality of life (QoL) were measured at baseline and weekly for 12 weeks. Data were analysed using means, range, standard deviations and proportions while independent t-test was used to compare the variables between the two groups.

Results: Demographic variables, baseline pain scores and quality of life between the 2 groups were similar. There was a statistically significant improvement in pain score in the Zoledronic acid group (1.38±0.53 vs 2.13±0.94) post-intervention, (p = 0.004).

Conclusion: The administration of three doses of Zoledronic acid at 4-weekly intervals significantly improved bone pain score during the 12-weeks follow up in patients with advanced prostate cancer.

Keywords: *Zoledronic acid, Bone pain, Prostate cancer.*

Correspondence: Dr. M.O . Akinwale, Department of Anaesthesia, College of Medicine, University of Ibadan, Ibadan. Nigeria E-mail: akinsmko@yahoo.com, moakinwale@com.ui.edu.ng.

Résumé

Contexte: Le cancer avancé de la prostate provoque souvent des douleurs qui peuvent être sévères nécessitant des soins palliatifs avec des analgésiques. L'acide zolédronique, un bisphosphonate de troisième génération, n'a pas été principalement utilisé comme adjuvant pour traiter la douleur chez les patients présentant des métastases osseuses secondaires à un cancer avancé de la prostate au Nigéria. L'étude a examiné les effets de 3 doses d'acide zolédronique, à des intervalles de 4 semaines, en plus du régime analgésique de morphine orale, de diclofénac, de paracétamol et d'amitriptyline, sur la douleur osseuse chez les patients atteints d'un cancer métastatique de la prostate.

Méthodes: Un essai prospectif randomisé ouvert dans lequel quarante patients souffrant de douleurs osseuses modérées à sévères dues à un cancer métastatique de la prostate ont été recrutés après approbation éthique de l'établissement. Les patients ont été répartis en deux groupes: Le groupe témoin (C) a reçu de la morphine orale liquide, du diclofénac, du paracétamol et de l'amitriptyline. Le groupe acide zolédronique (ZG) a reçu 3 doses d'acide zolédronique à intervalles de 4 semaines en plus de la morphine liquide, du diclofénac, du paracétamol et de l'amitriptyline. La sévérité de la douleur et la qualité de vie (QdV) ont été mesurées au départ et chaque semaine pendant 12 semaines.

Les données ont été analysées à l'aide des moyennes, de la plage, des écarts-types et des proportions, tandis qu'un test t indépendant a été utilisé pour comparer les variables entre les deux groupes.

Résultats: Les variables démographiques, les scores de douleur de base et la qualité de vie entre les 2 groupes étaient similaires. Il y avait une amélioration statistiquement significative du score de douleur dans le groupe acide zolédronique (1,38 ± 0,53 vs 2,13 ± 0,94) après l'intervention, (p = 0,004).

Conclusion: L'administration de trois doses d'acide zolédronique à des intervalles de 4 semaines a significativement amélioré le score de douleur osseuse au cours des 12 semaines de suivi chez les patients atteints d'un cancer de la prostate avancé.

Mots clés: *Acide zolédronique, douleur osseuse, cancer de la prostate.*

Introduction

Prostate cancer is one of the most common malignant lesions in male population and is the leading cause of cancer-related deaths in men [1,2]. It is the most commonly diagnosed cancer among Nigerian men [3]. In Nigeria, due to poor awareness among other reasons, many patients present late at advanced stage [4] and at times, pain may be the only reason some patients seek medical attention.

Bone is the most common and sometimes the only site for prostate cancer metastasis, which occurs in more than 80% of men with advanced disease [5] and this results in pain. Pain may also be due to perineal invasion or obstruction of lower end of ureter and prostatic urethra as a result of local invasion from the prostatic pathology [2]. Pain in patients with bone metastasis can be severe, progressive and burdensome, requiring palliation with analgesics. Such pain is often intractable to opioid therapy alone because of the multiple aetiology.

Causes of pain in bone metastasis include structural damage, mechanical stress, stretching of the periosteum, microfractures, reactive muscle spasm, pressure on adjacent nerves and tissues and release of chemical mediators like prostaglandin and cytokines [6]. Pain may be generalized, continuous or intermittent. It is usually described as aching, burning sensation, stinging or pulling. Metastasis-related pain is usually somatic but neuropathic pain may also occur as a result of pressure of tumour mass on the adjacent neural structures or invasion [2]. In addition to pain, bone metastasis from prostate cancer can also cause skeletal-related events (SREs) such as pathological fractures, spinal cord compression and abnormalities in serum calcium levels [2].

The treatment plan for metastatic cancer pain includes pharmacological and non-pharmacological methods. The main goal of treatment is to achieve optimal pain relief with minimum or tolerable side effects and to improve the quality of patients' daily life which is the main aim of palliative care. The World Health Organization proposed a 3-step analgesic ladder as a framework for pain management. This helps in providing effective treatment and reduces the side effects of the pharmacological agents [1]. Opioids are typically the most common drug used in the treatment of severe cancer pain. Morphine, an opiate first identified about 200 years ago, has been used to relieve pain for many years and its effectiveness has stood the test of time [7]. It induces analgesia by reducing neurotransmitter release presynaptically and hyperpolarizing dorsal horn neurons at the postsynaptic level, thus preventing rostral transmission of nociception [8].

Oral liquid morphine is the opiate of choice at the Hospice and Palliative Care unit of the University College Hospital (UCH), Ibadan, Nigeria since inception in 2007 and more than 1000 patients have used oral morphine principally to relief chronic severe pain. In line with WHO guidelines on the use of analgesic ladder for pain management, oral morphine [9] in combination with a non-steroidal anti-inflammatory drugs and paracetamol with an adjuvant are commonly used in our center.

As part of the armamentarium to control metastatic bone pain, bisphosphonate therapy, in addition to external beam radiation therapy, chemotherapy, radionuclide therapy and orthopaedic surgery, has been used [10]. Bisphosphonate therapy has emerged as an important component of the overall palliative therapy for malignant bone diseases. Bisphosphonates are synthetic analogs of a naturally occurring compound called pyrophosphates that prevent bone resorption and breakdown [11]. Examples of bisphosphonates in use are alendronic acid, pamidronate disodium, clodronate, ibandronate and zoledronic acid.

Of all the bisphosphonate agents available, zoledronic acid is the first to demonstrate significant and durable clinical benefit in reducing pain and skeletal complications for patients with malignant bone involvement from multiple myeloma and a variety of solid tumours including prostate cancer, breast cancer and lung cancer [12,13]. It is also useful in the prevention of bone loss associated with aromatase inhibitor therapy. However, osteonecrosis of the jaw (ONJ) is a relevant and specific complication of bisphosphonate therapy [14,15]. The diagnosis of bisphosphonate-related ONJ is primarily clinical based on the observation of nonhealing lesions involving exposed bone in the maxillofacial region. ONJ has also been recognized in association with radiotherapy, glucocorticoid use or following dental interventions [15].

In palliative care, the main focus of management is to improve the quality of life of patients who are suffering from life-limiting illnesses and this can be measured by using different performance status tools. Performance status is an attempt to quantify cancer patients' general wellbeing and activities of daily life [16]. It is a score that estimates the patient's ability to perform certain activities of daily living (ADLs) without the help of others. These ADLs include basic activities such as getting dressed,

eating, and bathing, as well as more complex activities such as cleaning the house and working a regular job [16,17]. It is a measure used to determine whether patients can receive chemotherapy, whether dose adjustment is necessary. In addition, it is also used in oncological randomized controlled trials as a measure of quality of life [16].

There are various scoring systems to determine the performance status of cancer patients. The common ones in use are Karnofsky score, Zubrod or the Eastern Cooperative Oncology Group (ECOG) score and Lansky score (for children). The Eastern Cooperative Oncology Group (ECOG) performance status (Zubrod score) describes a patient's level of functioning in terms of their ability to care for themselves, daily activity, and physical ability (walking, working, etc.) [16]. We chose to use ECOG (Zubrod) Performance status score in this study because of its simplicity and it has been validated for use in cancer patients [16,17].

The analgesic combination of oral morphine, non-steroidal, paracetamol and adjuvant are commonly used in the Hospice and Palliative care unit of our hospital. We chose to conduct this study to determine if the administration of 3 doses of zoledronic acid at 4-weekly interval will significantly reduce bone pain in patients with metastatic cancer of the prostate. Zoledronic acid was chosen over other bisphosphonates because it is more potent, has acceptable safety profile and tolerable.

Methods

This was a prospective randomized, open-labeled study. Upon obtaining approval from the University of Ibadan/University College Hospital (UI/UCH) Ethics Committee, forty consenting male patients with moderate to severe bone pain due to metastatic prostate cancer were recruited. Using the formula for comparing means, standard deviation of 1.5 in pain score from a previous study among cancer patients on oral morphine [9], statistical power of 90%, significant level of 5% and 10% attrition rate, the minimum sample size was 40.

Inclusion criteria were pain score ≥ 6 (NRS), biopsy-confirmed prostate cancer, bone metastasis confirmed by radioisotope bone scans and patients living within the catchment area (not more than 20km from the hospital). Excluded from the study were patients with history of gastritis or peptic ulcer disease, expected time to live of less than 3 months, allergy to study drugs, patients with prior bisphosphonate therapy within 6 months of enrollment and patients living outside catchment area during the study period. In addition, patients that refused to give consent, previous radiation therapy within one month of enrolment, and patients with active dental problems (for Zoledronic acid group) were excluded from the study.

At study entry, details of the study protocol were explained to the patients in the language they understood. Relevant history relating to bone pain (onset, duration, intensity, locations and other characteristics) was taken and patients were taught how to rate their pain using the pain ruler with the 11-point numerical rating scale (NRS 0 – 10). The baseline pain score was documented before initiating treatment and pain was assessed during treatment and documented weekly during the study period. Patients were also educated on oral morphine use with a view to dispel the myths surrounding morphine use in chronic pain management.

In addition, the main caregivers of each patient was taught pain assessment using the same pain ruler. The main carers were then asked to rate pain intensity of their patients. The main carer in this study was defined as an individual (e.g. spouse, child, relation) who has been involved in the daily care and lived with the patients for at least 3 months consecutively.

Patients were randomly assigned to two treatment groups using the table of random numbers generated by a statistician into: Control (CG) and Zoledronic (ZG) groups. Each patient was asked to pick from an envelope with sealed allocation either Control (CG) or study group (ZG). Patients in the control group received oral morphine 5mg every 4 hours and 10mg at night, diclofenac tablet 50mg every 12 hours and paracetamol tablet 1gm three times daily. The study group, ZG received intravenous infusion of 4mg Zoledronic acid every four weeks for 3 months in addition to oral morphine, diclofenac and paracetamol tablets in dosages stated above. We chose to use 4-weekly infusion of zoledronic acid as previous study by Himelstein et al which explored the possibility of longer interval (12-weekly) administration of zoledronic acid instead of standard 4-weekly infusion concluded that reduction in pain and skeletal-related events did not differ significantly between the 2 dosing intervals [18].

Initial enrolment and assignment of participants into intervention groups took place either at the Urology clinic or Hospice and Palliative care unit by the Principal investigator and the Medical officer, who is a member of the research team

In line with the practice at the Hospice and Palliative care Unit of the hospital, an individualized and gradual approach to changes in dosage of oral morphine, and other analgesics was employed to

forestall any unwanted effects. The dose of liquid morphine and other analgesics were adjusted according to degree of pain control and patient's physiological response. Patients in the Zoledronic acid group had 4mg of Zoledronic acid added to 100mls of normal saline and infused through a peripheral vein over 15 minutes. For breakthrough pain, 2.5-5mg of oral morphine was given as required. All patients had analgesic adjuvant antidepressant, amitriptyline 12.5 – 25mg to control the neuropathic component of metastatic bone pain.

Based on the pilot study, we found it difficult documenting pain score and amount of study drugs consumed on a daily basis. The reasons include the fact that some of these patients were treated on outpatient basis and some patients and their caregivers could not religiously keep daily pain score charts. In addition, making contact with some patients through the telephone for pain assessment was not encouraging. Therefore, patients were asked to give the average level of pain relief using NRS pain score over a week period and such was documented. Also, the total dose of morphine, diclofenac, paracetamol and amitriptyline consumed weekly was determined by subtracting the amount consumed from the amount supplied on weekly basis.

To prevent constipation, a common complication of oral morphine, each patient received tablet Dulcolax (Bisacodyl), a laxative, 10 mg once or twice daily. Liquid paraffin was also given when necessary. Nausea and vomiting was treated with metoclopramide 10mg twice daily.

All patients had haemoglobin or packed cell volume levels determined at baseline while patients in the zoledronic acid group had serum creatinine, calcium and phosphate levels determined before commencement of treatment in compliance with the treatment guidelines for zoledronic acid therapy in patients with bone metastasis [19]. In addition, patients in ZG group were evaluated by the dentist to assess for dental health prior to administration of zoledronic acid infusion to prevent osteonecrosis of the jaw, a side effect of bisphosphonate administration

To prevent gastric erosion from diclofenac, patients were advised to take antacid and to use medications after meals. All other treatment excluding pain management was at the discretion of the managing Urologists.

Baseline pain score using NRS (0-10) and the quality of life using Eastern Cooperative Oncology Group were assessed by the investigators at the study entry, and at weekly follow up clinic visit or at each scheduled home visit for 12 weeks. The parameters used to assess the quality of life included reduction in pain level to patient's acceptable level and at least one-point reduction in ECOG performance status.

The Eastern Cooperative Oncology Group (ECOG) score runs from 0 to 5, with 0 denoting fully active, able to carry on all pre-disease performance without restriction. 1 denotes patients who are restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work ; 2-Patient is ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours; 3- Patient who is capable of only limited self-care; confined to bed or chair more than 50% of waking hours; 4-Completely disabled patient who cannot carry on any self-care and totally confined to bed or chair while a score of 5 denotes a dead patient [16].

To ensure adequate follow up, only patients within the catchment area were recruited. However, it was not possible to adopt a uniform pattern of follow ups, so patients were followed up weekly either at the Urology clinics, at the Palliative care unit, at home (for those on home-based care) or on the wards (those admitted for other medical reasons) and via phone calls. Drug dosage adjustments were done based on each patient's response to pain treatment and pain score during the follow-ups.

Safety of the patients was assessed by evaluating all adverse events throughout the study period and by evaluating all laboratory tests, when necessary. All drugs, intravenous fluids and other accessories used in this study were obtained through the Stores and Pharmacy Departments of the University College Hospital, Ibadan, Nigeria.

The primary outcome measure was the reduction in mean pain score using NRS. The secondary outcome measure is the improvement in the quality of life parameters using ECOG performance status score. In addition, data on skeletal-related effects or complication due to metastasis to spine and lower limbs including spinal cord compression, pathological fractures and needs for radiation to bones were collected.

Results

All forty patients recruited completed the12-week follow up period. Patients' demographics and baseline pain characteristics were similar (Table 1). The mean age (±SD) in both groups were similar: 71.35 ± 9.2 vs 71.96 ± 7.7 years (p=0.824). The average duration of pain before presentation at the hospital was 95.35 ± 9.98 and 111.65 ± 9.82 days for Control and

Zoledronic groups respectively (p =0.61). Baseline pain score rated by the patients using NRS was 8.45 ± 0.83 for the Control group and 8.40 ± 0.94 for the Zoledronic group (p = 0.86). This was not significantly different from the pain score rated by the caregivers, 8.88 ± 0.81 vs 8.83 ± 0.147 for Control and Zoledronic group respectively (p = 0.93). Patients' expected and acceptable level of pain at the time of enrolment for study was also similar in the 2 groups: 1.65 ± 0.59 vs 1.55 ± 0.51(p = 0.57). Patients' quality of life assessed at study enrolment using ECOG score were also similar in the 2 groups: 3.35 ± 0.59 vs 3.25 ± 0.72 for Control and Zoledronic group respectively (Table 1).

Number of sites of pain in both groups did not differ significantly (Table 2). 85% of patients in Control group experienced pain in 3 sites or more while 70% had pain in 3 sites or more in the Zoledronic acid group. As expected, pelvic, lumbo-sacral regions and femur were the commonly pain location in both groups.

During the 12-week period, patients in Zoledronic acid group had a statistically significant improvement in pain control with a mean pain score of 1.38± 0.53 as against 2.13 ± 0.94 for Control group (p = 0.004) (Table 3). The change in mean pain score during the weekly follow-up is as shown in Figure 1. All patients in the 2 groups had a 1-point reduction in ECOG performance status score and the quality of life did not differ significantly (p > 0.160).

The total dose of morphine, diclofenac, paracetamol and amitriptyline consumption during the 12 weeks were statistically insignificant in both groups (Table 4). In addition, spinal cord compression with varying degrees of lower limb weakness, sensory loss and difficulty with ambulation was observed in the 2 groups. (Fig.2)

Discussion

Prostate cancer is the most commonly diagnosed non-cutaneous cancer among Nigerian men [4]. Pain is a major accompaniment of metastatic prostate cancer and many patients develop varying degrees of pain in the course of the disease. At times, pain may be the only reason some patients seek medical attention. Skeletal pain is one of the most burdensome and difficult to treat aspects of metastatic bone disease

Table 1: Patients demographics and baseline pain characteristics

Characteristics	Control Group	Zoledronic Acid Group	P-Value
Age (years) ±SD	71.35 ± 9.2	71.95 ± 7.7	0.824
Duration of pain before enrolment (days) ±SD	95.35 ± 9.98	111.65 ± 9.82	0.61
Baseline pain score (NRS): rated by patients ±SD	8.45 ± 0.83	8.40 ± 0.94	0.86
Baseline pain Score - rated ny the Carers ±SD	8.88 ± 0.81	8.83 ± 0.147	0.93
Patients acceptable Level of Pain ±SD	1.65 ± 0.59	1.55 ± 0.51	0.57
Baseline ECOG Score ±SD.	3.35 ± 0.59	3.25 ± 0.72	0.54

Table 2: Location of pain

Location	Control Group	Zoledronic Group	P-Value
Pelvis	19 (95%)	19 (95%)	1.00
Lumbo-Sacral	16 (80%)	17 (85%)	0.677
Femurs	18 (90%)	16 (80%)	0.658
Humerus	5 (25%)	3 (15%)	0.693
Ribs (Chest)	5 (25%)	1 (5%)	0.184
Skull	0	1 (5%)	1..00
Others (Abdomen, Hands, Foot)	3 (15%)	3 (15%)	1.00

Table 3: Post-treatment characteristics

Variable	Control Group	Zoledronic Group	P-Value
Pain Score ±SD	2.13 ± 0.94	1.38 ± 0.53	0.004
ECOG Score ±SD	2.68 ± 0.56	2.40 ± 0.67	0.160
Total Number Days Spent in the Study ±SD	100.45 ± 29.8	106.35 ± 24.33	0.497

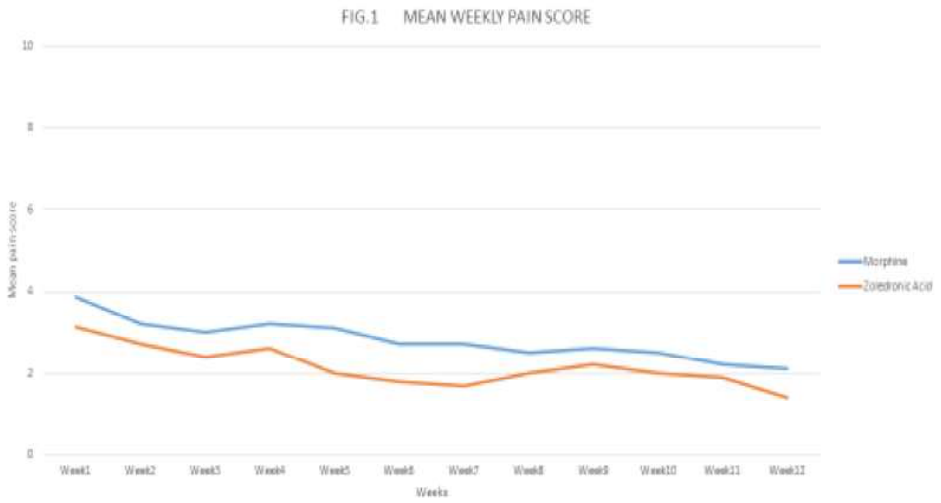
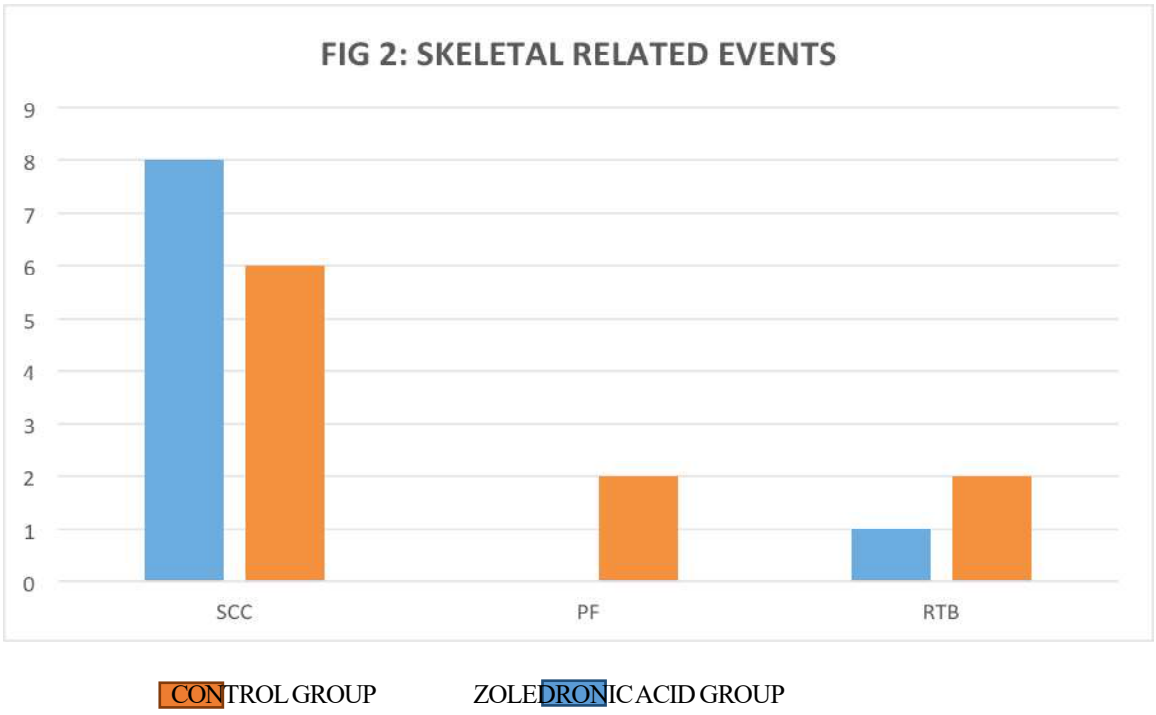


Fig. 1



SCC- Spinal Cord Compression
PF- Pathological Fracture

Table 4: Total (Mean) drugs consumption over 12-week period

Medication	Control Group	Zoledronic Acid Group	P-Value
Morphine ±SD (MG)	2116.85 ± 272.0	2053.50 ± 166.0	0.380
Diclofenac ±SD (MG)	1465.0 ± 126.80	1515.0 ± 328.1	0.529
PCM ±SD (G)	68.55 ± 6.5	51.6 ± 9.7	0.00
Amitriptylline±SD(MG)	1380.17 ± 382.79	1273.13 ± 355.0	0.365

[20]. We investigated the effects of zoledronic acid on bone pain control and quality of life of Nigerian men with advanced prostate cancer.

All patients recruited for this study presented with severe pain (NRS mean 8.43, range 7-10) and the median duration of pain before presentation was 75 (2-365) days. This shows that patients in this study presented late to the hospital for pain control and this may be a reflection of patients' attitude in developing or resource-poor countries in seeking medical attention. This may be attributed to ignorance, lack of screening programmes and poverty, late referral by the primary physicians among other reasons [21].

In pain management, it is not uncommon for some patients or their caregivers to exaggerate pain severity during pain assessment probably to get immediate attention. This was not observed in this study as the pain scores rated by the patients and their carers did not differ significantly. In addition, the acceptable levels of pain at presentation were similar in the 2 groups. It is a common practice in the Hospice and Palliative Care of our hospital to determine each patient's acceptable level of pain at presentation. This helps the physician to tailor the management modalities for individual patient and also helps to assess the success of such treatment.

Majority of patients in both groups had pain involving the pelvic, lumbo-sacral regions and femurs. This is expected as these bony structures are common areas of metastasis due to their close proximity to the prostate gland.

At the end of the 12-week follow-up period, patients in the zoledronic acid group had a clinically significant reduction in pain score compared to patients in Control group. Various studies have attested to the efficacy of zoledronic acid in producing a significant pain relief in metastatic bone pain [22-24]. Nakamura *et al* [22] achieved improvement in bone pain control in 82.4% of Japanese men who were previously treated with morphine and NSAIDS with zoledronic acid administration. Furthermore, Saad observed that zoledronic acid provided a significant long-term reduction in bone pain when compared to the placebo [23] and Kmetec *et al* [24] reported satisfactory pain reduction, reduced analgesic consumption and satisfactory safety profiles with zoledronic acid. In order to derive full benefit, Gravalos [19] and El-Amim [25] recommended that zoledronic acid should be administered early in the disease when bone metastases are detected, even if the patient is asymptomatic and that it should be continued during the course of the disease.

At baseline, we found that the quality of life of patients using the ECOG performance status score was Ã3 in the 2 groups. ECOG score of >3 indicates patient who is capable of only limited self-care and confined to bed or chair 50% or more of waking hours [16]. In contrary to our finding, Nieder et al reported a better baseline performance status of ECOG 1(range 0-2) [25] and this was attributed to early presentation of cancer patients to the hospitals. The unsatisfactory baseline ECOG scores reported in our study could be attributed to the fact that, in our environment, patients with cancer of the prostate seek medical attention late thereby presenting in advanced stages of the disease. This may be due to poor awareness of palliative care services, poverty, illiteracy, ignorance, cultural and religious factors among patients.

In addition, primary physicians do not refer cancer patients early for palliative care and this often results in patients presenting at the advanced stage of the disease. This practice negates the recommendation for early palliative care team involvement in cancer care which should start early in the diagnosis process, ideally within 8 weeks of diagnosis and should continue throughout the disease trajectory [26]. Late referral may be attributed to the lack of knowledge on benefits of palliative care among health care professionals even when palliative care services are readily available and despite the fact that some patients have a positive attitude towards palliative care and hospice services [27].

Skeletal-related events (e.g. pathological fracture, spinal cord compression, and need for radiation to bones) are common complications of bone metastases in advanced prostate cancer [28]. The Urologists primarily use bisphosphonates such as zoledronic acid to prophylactically prevent these complications. Studies have shown that zoledronic acid reduces all types of skeletal related events compared to placebo in cancers, metastatic to bone, by 36% [23,28,29].

During the 12-week observation period, no patients in the Zoledronic acid group had pathological fracture. However, two patients (10%) in the Control group had pathological fractures which was not statistically significant. 8 patients (40%) in the zoledronic acid group and 6 patients (30%) in the Control group had symptoms suggestive of spinal cord compression which included varying degrees of limb weakness, difficulty walking and sensory loss. Metastatic spinal cord compression is a well-recognised complication of cancer especially prostate, breast and lung cancer. It occurs when there is collapse or compression of diseased vertebral body or direct tumour extension into the vertebral column [29]

A potential risk associated with the use of bisphosphonates is osteonecrosis of the jaw (ONJ) which is a localized death of bone tissue of the jaws. It is a rare potential complication in cancer patients receiving treatments including bisphosphonate, radiation, chemotherapy, or in patients with tumors or infectious embolic events[30]. Patients with multiple myeloma and those with metastatic skeletal disease who receive bisphosphonate therapy usually have the highest risk of developing ONJ [14,28]. Whereas exposure of bone is characteristic, it may be absent in early stage of the disease in up to 45% of cases [29]. Single Photon Emission Computed Tomography (SPECT) bone scan alone or in combination with Computed Tomography (CT) is useful in the early non-invasive detection of ONJ although it has its limitations [15,31]. Panoramic radiographs, CT, MRI are also useful radiologic tests in the imaging of ONJ.

We did not record any incidence of ONJ in patients in the Zoledronic acid group during the 12-week study period. This may be as a result of short duration of zoledronic acid administration and/or short follow-up period. Another reason may be that we carefully chose patients for the study as we ensured that all patients recruited into the zoledronic acid group had pre-recruitment normal serum calcium and phosphate levels in compliance with the recommendations for zoledronic acid treatment of patients with bone metastasis [24]. In addition, all patients were reviewed by the Dentists to ensure that they were dentally fit.

Patients in this study received 3 infusions of zoledronic acid at 4-weekly intervals and were followed up for 12 weeks only. Studies have shown that incidence of ONJ depends both on the duration of bisphosphonate administration and the duration of follow up. Bamias *et al.* [32] reported the incidence of 6.7% and concluded that the incidence of ONJ increased with time of exposure to bisphosphonates from 1.5% among patients treated for 4 to 12 months to 7.7% for treatment of 37 to 48 months. Woo-Sung *et al.* [33] reported an incidence of 6.9% in a population of 130 patients and the median administration time of bisphosphonate was 19 months.

Other side effects such as constipation, sedation, nausea and vomiting were not significantly different in the two groups.

In conclusion, the administration of three doses of Zoledronic acid at 4-weekly interval significantly improved bone pain score during the 12-week follow up in patients with metastatic prostate cancer. Improvement in the quality of life of patients in both groups was similar.

Limitations of the study

The limitations of this study included the fact that the investigators and patients were not blinded to the study drugs and this is a source of bias. Average pain score was determined on weekly basis and this introduced a recall bias. In addition, use of crude method to determine the quantity of drugs consumed weekly, small sample size, short duration of zoledronic acid administration and short observation period of patients were other limitations.

Recommendations

We recommend that study should be conducted to determine if the administration of zoledronic acid in the early stage of cancers with predilection to bone metastasis (such as prostate and breast cancers) will reduce the incidence of skeletal-related events, especially, pathological fractures and spinal cord compression. The study should also incorporate a long-term follow-up period to assess effects of longer duration of administration of zoledronic acid including the development of osteonecrosis of the jaw.

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