Journal of Bone Oncology 8 (2017) 13–17

Contents lists available at ScienceDirect

Journal of Bone Oncology

journal homepage: www.elsevier.com/locate/jbo

Research paper

Complications of bone metastases from malignant melanoma

Jamal Zekri[a,b,*], Maria Marples[c], Dominic Taylor[c], Kiran Kandukurti[d], Lucy McParland[e], Janet E. Brown[f]

[a] Weston Park Hospital, Sheffield S10 2SJ, England, UK
[b] Al-Faisal University, King Faisal Specialist Hospital & Research Centre, Jeddah, Saudi Arabia
[c] St James's Institute of Oncology, St James's University Hospital, Leeds LS9 7TF, UK
[d] Weston Park Hospital, Sheffield S10 2SJ, England, UK
[e] Clinical Trials Research Unit, Leeds Institute of Clinical Trials Research, University of Leeds, Leeds LS2 9PH, UK
[f] Academic Unit of Clinical Oncology, University of Sheffield, Weston Park Hospital, Sheffield S10 2SJ, England, UK

ARTICLE INFO

Keywords:
Melanoma
Bone metastases
Skeletal related events

ABSTRACT

Introduction: Metastatic bone disease (MBD) carries significant morbidity for patients with cancer. MBD from malignant melanoma (MM) is understudied. We examined the characteristics, morbidity, management and outcome of MBD in patients with MM.

Methods: Patients with metastatic MM managed at two referral cancer centres in England were identified. Those with bone metastases (BMs) were selected. Patient and disease characteristics including skeletal related events (SREs) were extracted from medical records. The Kaplan Meier method was used to calculate median survival.

Results: Five hundred and eighteen patients with metastatic MM were managed between years 2000 and 2008. Eighty nine (17.2%) patients had BMs and are the subject of this study. Median age at diagnosis was 53 years and 55% were males. BMs were identified at the time of diagnosis of metastatic disease in 68.5% patients. Sixty-six (74.2%) had multiple bone lesions and 80.9% had axial skeleton involvement. One hundred and twenty nine skeletal related events occurred in 59 (66.3%) patients (50 radiotherapy, 28 hypercalcaemia, 20 bone fractures, 18 spinal cord compression and 13 orthopaedic surgery). The annual skeletal morbidity rate was 2.5.

Median survival from diagnosis of BMs was 17.3 weeks and was 5.6 weeks from the first episode of hypercalcaemia.

Conclusion: MBD affects a clinically important proportion (17.2%) of patients with metastatic MM. It carries a substantial morbidity and mortality exceeding that caused by BMs from breast and prostate cancer. These patients should receive the currently licensed bone modifying agents and should be included in clinical trials addressing MBD.

1. Introduction

The incidence of malignant melanoma (MM) is increasing worldwide [1]. Recently developed biological therapies have improved survival of patients with advanced and metastatic disease. However, the prognosis for these patients remains poor with median overall survival shorter than 1.5 years [2]. Melanoma patients with soft tissue (including skin and lymph nodes) or lung metastases and normal lactate dehydrogenase fare better than those with metastases elsewhere (e.g. liver, brain) and/or raised LDH [3].

Bone is a frequent site for metastases in patients with some of the common malignancies including breast, prostate and lung cancer. However, bone metastases (BMs) are more common than often realized in a range of other malignancies [4]. BMs can cause substantial morbidity and skeletal complications, referred to as skeletal related events (SREs) including pathological fractures of bones, spinal cord compression, hypercalcaemia, radiotherapy and surgery to bone (as treatment for BMs). It is estimated that across all tumour types, one of these major skeletal events occurs on average every 3–6 months [5].

A large series from Duke University Medical Centre reported BMs in 6.9% of 1677 patients diagnosed with all stages MM between the years 1956 and 1976 [6]. Mean survival from the diagnosis of bone metastases of was 3.6 months suggesting that clinically overt BM from melanoma become apparent towards the end of the disease's trajectory when rigorous investigation and aggressive interventions may be considered unjustified [6].

* Corresponding author at: Weston Park Hospital, Sheffield S10 2SJ, England, UK.
E-mail addresses: jmzekri@hotmail.com (J. Zekri), maria.marples@nhs.net (M. Marples), dominic.taylor@nbt.nhs.uk (D. Taylor), kiran.kandukurti@gmail.com (K. Kandukurti), l.mcparland@leeds.ac.uk (L. McParland), j.e.brown@sheffield.ac.uk (J.E. Brown).

http://dx.doi.org/10.1016/j.jbo.2017.08.003
Received 21 May 2017; Received in revised form 8 August 2017; Accepted 10 August 2017
Available online 18 August 2017

MBD from MM remains an under-investigated subject. More recent series have concentrated on special cases such as isolated skeletal metastases and specific anatomical bone site metastases [7,8]. In addition, with the recent improvement in diagnostic and therapeutic landscape including bone modifying agents, metastatic bone disease (MBD) is gaining more attention. We therefore conducted a retrospective study to examine the characteristics, morbidity, management and outcome of MBD in patients with MM managed in Yorkshire, UK.

2. Methods

2.1. Patient selection and extraction of data

The study was conducted at two regional referral oncology centres in West and South Yorkshire, UK, namely St. James's University Hospital, Leeds and Weston Park Hospital, Sheffield.

The study period was January 2000 - March 2008 for the Leeds centre and January 2000 – December 2005 for the Sheffield centre. Records of all patients registered with diagnosis of any stage MM in these periods were screened (Leeds: 1716 and Sheffield: undocumented) and those with metastatic disease (n = 518) were identified. Of these, patients with BMs were selected and are the subject of this study. Paper and electronic records of these patients were reviewed in detail. Patients' and disease characteristics were extracted.

2.2. Clinical classifications

The distribution of BMs was classified as axial (skull, thoracic cage and vertebral column) or appendicular (shoulder girdle, pelvic girdle and limb bones). Radiology imaging reports were carefully reviewed to establish and confirm the diagnosis and distribution of bone metastases. Review of imaging films (when available) was performed to clarify imaging reports only if indicated. SREs were identified. Hypercalcaemia was defined as adjusted serum calcium > 2.60 mmol/l. After treatment of hypercalaemia, a recurring event was diagnosed if serum calcium rises again above 2.60 mmol/l or if it rises above any post-treatment above normal value. Pathological fractures of bones, spinal cord compression and surgery to bone (as treatment for BMs) were counted on anatomic basis. For example, 2 synchronous or metachronous bone fracture or surgeries to bones were counted as 2 separate SREs even if they involved one bone. Radiotherapy in 2 different fields to 2 different bone sites were counted as 2 separate SREs even if radiotherapy was delivered during the same period. Treatment of SREs was also recorded.

2.3. Statistical analysis

Duration of follow-up was defined as the time from diagnosis of melanoma until date of death or date patient was last seen alive. The Kaplan-Meier method was used to plot the survival distributions and estimate the median survival times for the time from diagnosis of melanoma, diagnosis of BMs, and first episode of hypercalcaemia to death. Patients who were still alive at the time of the audit, were censored at the date they were last known to be alive. The skeletal morbidity rate (SMR) was defined as to the number of SREs reported, divided by the person-years at risk i.e. time from diagnosis of BMs to death / last seen alive.

All analyses were carried out in SAS version 9.4.

3. Results

Medical records of 518 patients with metastatic MM were reviewed (409 in Leeds and 109 in Sheffield). Eighty nine patients (17.2%) with BM (70 in Leeds and 19 in Sheffield) were identified. The median follow-up time of these 89 patients from initial diagnosis of MM was 2.2 years (range: 0.1–22.7).

Table 1 presents the patient and disease characteristics. The median age at first diagnosis of MM was 53 years (range: 22–93) and 49 (55.1%) were males. For the majority of patients, the primary site of disease was cutaneous (n = 67, 75.3%).

Table 1
Characteristics of malignant melanoma patients with bone metastases (n = 89).

Gender	
Males	49 (55.1%)
Females	40 (45.9%)
Age at primary diagnosis of MM	
Median (range)	53 (22–93) years
Primary site of MM	
Cutaneous	67 (75.3%)
Mucosal or unidentified	12 (13.5%)
Ocular	8 (9.0%)
Acral	2 (2.2%)
Bone metastases present at diagnosis of primary disease	
Yes	6 (6.7%)
No	83 (93.3%)
Bone metastases present at diagnosis of metastatic disease	
Yes	61 (68.5%)
No	28 (31.5%)
Time between primary diagnosis of MM and bone metastases Median (range)	1.8 (0.0 – 19.6) years
Frequency of bone metastases	
Single	23 (25.8%)
Multiple	66 (74.2%)
Sites of bone metastases	
Only axial	47 (52.8%)
Only appendicular	17 (19.1%)
Axial and appendicular	25 (28.1%)
Patients experiencing SREs	59/89 (66.3%)
Radiotherapy	45 (50.6%)
Hypercalcaemia	20 (22.5%)
Bone fracture	17 (19.1%)
Spinal cord compress	18 (20.2%)
Surgery to bones	12 (13.5%)

Six patients (6.7%) presented with BMs at diagnosis of the primary disease, whilst the remainder developed BM after their initial melanoma diagnosis with a median time of 1.8 (range: 0–19.6) years.

BMs were identified at the time of initial diagnosis of metastatic disease in 61 (68.5%) patients and later (median 2 months) in the remaining 28 (31.5%). Sixty-six patients (74.2%) had BM at multiple sites.

Fifty-nine patients (66.3%) experienced one or more SRE with over 50% of patients requiring radiotherapy (Table 1). In total 129 SREs were reported as follows: need for radiotherapy (n = 50), hypercalcaemia (n = 28), bone fractures (n = 20), spinal cord compression (n = 18) and orthopaedic surgery (n = 13), representing 38.8%, 21.7%, 15.5%, 14% and 10% of all reported events respectively (Fig. 1).

Twenty patients (22.5%) developed 28 episodes of hypercalcaemia, of which 11 patients (55%) received therapeutic bisphosphonates. The remaining patients received other therapies, had mild chemical asymptomatic hypercalcaemia or were too unwell for specific treatment. An additional 16 patients (17.9%) received bisphosphonates primarily for the management of bone pain.

The annual skeletal morbidity rate was 2.5 (95% CI: 2.1, 2.9) i.e. 2.5 SREs are reported per patient for every year of follow-up.

Four patients were still alive at the time of data collection were censored in the analyses. The median survival of all patients from the diagnosis of BMs was 17.3 weeks (95% CI: 11.3–20.4), with a probability of survival at one year of 8% (Fig. 2). Median survival was 5.6 weeks after the first episode of hypercalcaemia (95% CI: 3.0–12.7).

4. Discussion

We reviewed patients with BMs from MM registered at two tertiary