

Research paper

Complications of bone metastases from malignant melanoma



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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].

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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 hypercalcaemia, 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

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%)

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%).

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

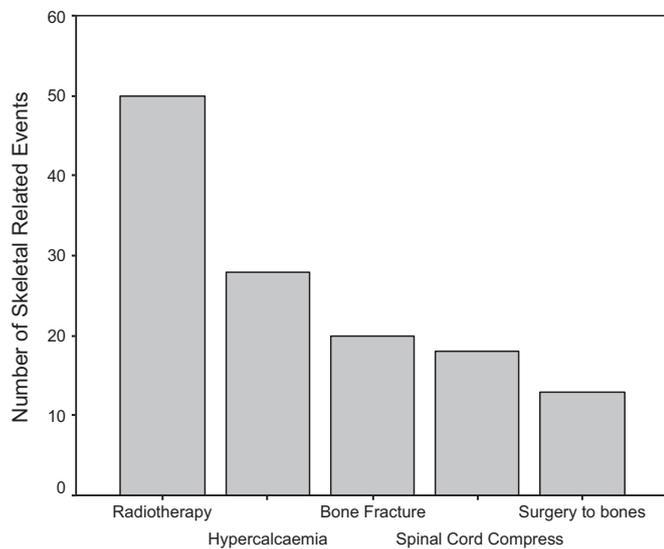


Fig. 1. Distribution of 129 reported skeletal related events.

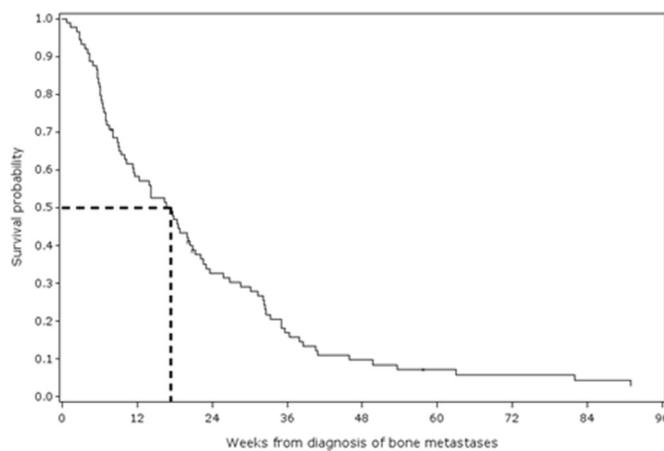


Fig. 2. Overall survival in weeks from diagnosis of bone metastases.

referral cancer centres in Yorkshire. The findings of this study are intended to shed light on the behaviour and outcome of BMs from MM in the era when cytotoxic chemotherapy and biological therapies (mostly interferon) were the standards of care.

The crosstalk between bone, tumour cells, and immune cells is well-studied. However, radiological response to systemic anti-cancer therapy in BMs is less frequently observed than that in soft tissue. This could at least partly be due to immune escape by disseminated tumour cells in the BMs micro-environment [9]. Our findings will serve as background for future studies in the current era of targeted therapies, immunotherapy and checkpoint inhibitors.

The total number of screened cases with all stage MM was not documented in the Sheffield cohort and was 1716 in the larger Leeds cohort. The frequency of BMs in patients with all stages in the Leeds cohort was 4.1% (70/1716). This is in line with 6.9% (116/1677) in patients diagnosed with MM at Duke University Medical Centre between the years 1956 and 1976 [6].

This frequency reflects the culture where investigations for BMs are performed only in patients with suspicious symptoms. In addition, isotope bone scans are recognized to yield false-negative results in 15% of cases [8]. The true frequency may be higher than reported here. Indeed, in one study on autopsy, 48.6% of patients with metastatic MM were found to have BMs [10].

The aim of our study was to investigate BMs in patients with metastatic MM. We found that BMs were diagnosed in 17.2% of patients

with this stage of disease. In accordance with guidelines for the procedures of referral to site-specific multi-disciplinary teams, we expect that the vast majority of patients with metastatic MM in the patient population studied were referred to one of these two cancer centres suggesting this figure is robust [11]. Similarly, another retrospective review of CT scans in 98 patients with metastatic MM reported BMs in 17 (17.3%) [12].

Around two thirds of patients in our study had BMs at the initial time they were diagnosed with metastatic MM. This finding suggests that patients diagnosed with metastatic disease at any site should be fully staged as there is a high chance of coexistence of other distant metastases.

Generally, ocular and mucosal melanomas represent 3.7% and 1.4% of all primary melanomas respectively [13]. In our series 9% and 13% of patients with BMs had ocular and mucosal primaries respectively. This observation suggests that ocular and mucosal melanomas have higher propensity than cutaneous melanoma to metastasize to bones. However, this conclusion may be limited by the lack of detailed information of the all stages screened population.

Majority of patients (80.9%) developed BMs in the axial skeleton (52.8% axial alone and 28.1% axial and appendicular). Predominance of BMs from melanoma to the axial skeleton has been previously reported in 80% of 50 patients with BMs from MM [14].

Our results confirm the dismal natural history of these patients with median survival of 17.3 weeks from the diagnosis of BMs and one year survival of 8% (Fig. 2). There is a paucity of survival outcome data for these patients in the literature. In a retrospective review of 428 patients with recurrent melanoma, patients with metastases in the liver, CNS, bone and multiple-sites distant disease had shorter survival compared to those with distant skin, distant lymph node, or pulmonary metastases as first metastatic sites. The median survival of patients with bones as first site of metastasis was 2.4 months (10.4 weeks) and the one year survival was 10% (data extracted from reported survival curves) [15]. A mean survival time of 4.7 months was reported for 30 patients diagnosed with BMs from MM 25–35 years ago in Los Angeles [14].

Care of patients with high risk and advanced MM in West and South Yorkshire is centralized in 2 tertiary care referral centres in Leeds and Sheffield respectively. Consequently, the vast majority of SREs would have been captured in patients’ records at one of these 2 centres.

Fifty nine (66.3%) of our patients experienced one or more SREs. In comparison, SREs are reported in 52–64% (no bisphosphonates) and 31–51% (on bisphosphonates) of patients with BMs from breast cancer [16,17]. This indicates that BMs from MM carry similar or even higher morbidity than that from breast cancer considering the shorter survival of patients with metastatic MM. In addition, SREs are well recognized to have a detrimental effect on physical, emotional and functional well-being [18].

Hypercalcaemia was the commonest metabolic complication seen in patients with advanced cancer prior to the era of widespread use of bisphosphonates for MBD.

Hypercalcaemia is diagnosed in 1.1% of all stage MM. It is associated with multiple bone and visceral metastases in the majority of patients [19,20].

Hypercalcaemia was reported in 56/1146 (4.9%) patients with metastatic melanoma treated at the American National Cancer Institute between years 1988 and 2000 [21].

There was no specific frequency of clinical follow up. Generally, all patients with metastatic MM attending the study centres were under regular clinical follow up at variable intervals guided by clinical need. Biochemical tests including serum calcium measurement were routinely performed every few weeks (mostly every 3 weeks) for patients on systemic therapy and less frequently (mostly every 6–8 weeks) for those who were not.

Our results show that hypercalcaemia is a frequent complication developing in 22.5% of patients with BMs from MM. This is higher than its frequency in patients with BMs from breast cancer (8.8–13%; no

bisphosphonates) and (2.6–6%; on bisphosphonates) [16,17].

We confirmed the poor outcome of patients with hypercalcaemia and MBD from MM with median survival of less than 6 weeks. This is in line with the median survival of 30 days reported earlier [20]. It is clear that MBD and hypercalcaemia in these patients carry a dismal survival outcome despite brief correction of calcium level after treatment with hydration and bisphosphonate [20].

There is recognized association between SREs (e.g. pathological bone fractures) and increased risk of death in patients with other solid tumors [22]. It is reasonable to suggest that survival may be improved if this terminal event (hypercalcaemia) and other SREs are delayed or prevented. Bisphosphonates, in particular Zoledronic acid (ZA) delay the development of SREs [4]. In a randomised phase III trial, 773 patients with BMs from solid tumors (other than breast and prostate; including 15 patients with melanoma) were randomized to receive ZA or placebo. Fewer patients treated with ZA developed SREs at 21 months. Furthermore ZA significantly delayed the median time to first SRE (236 vs. 155 days; $P = 0.009$) [23].

Denosumab is a human monoclonal antibody against receptor activator of nuclear factor κ B ligand (RANKL). It is licensed for the prevention of SREs in adult patients with BMs from solid tumors. Among patients with solid tumors other than breast and prostate, denosumab delayed the time to the first on-study SRE more effectively than ZA [24].

Based on the efficacy of these bone modifying agents, we recommend the early use of denosumab or ZA in patients with BMs from melanoma before the development of SREs. This approach may improve quality of life by delaying and reducing the occurrence of SREs. At the same it may improve survival by delaying the pre-terminal event of “hypercalcaemia”. Actively pursuing the detection of BMs as soon as recurrent or metastatic disease is diagnosed will facilitate earlier administration of bone modifying agents and may enhance their potential benefits.

Eleven of our patients received bisphosphonates for hypercalcaemia while others received them for other complications of MBD (e.g. pain). Due to the retrospective nature of this study, we were unable to ascertain the exact indications and efficacy in some of these patients. In addition, many of these patients had poor survival and were often discharged to hospices or community palliative care teams precluding detailed follow up.

There is an increasing body of evidence suggesting that bisphosphonates exhibit anti-tumour properties [25]. Results of two large clinical trials and a recent meta-analysis support this notion in postmenopausal (natural or medically induced menopause) women with breast cancer [26–28].

There is *in vitro* and *in vivo* evidence that ZA induces death of melanoma cells [29]. Certainly, there are no strong clinical data to support this notion in the clinical setting. However, colleagues from London (UK) reported a case of metastatic MM treated with ZA (without systemic anti-cancer therapy) and achieved complete clinical and radiological response at all metastatic site (bones and lungs). This response lasted for 23 months. Peripheral blood mononuclear cells studies in this patient suggested that ZA mediated activation of V γ 9V δ 2 gamma-delta T cells to be a possible explanation [30].

RANKL may play an important role in development of BMs from MM. *In vitro* studies show that melanoma tumour associated macrophages differentiate into osteoclasts in the presence of RANKL [31]. Cas Interacting Zinc Finger Protein/ Nuclear Matrix Protein4 (CIZ/NMP4) is a transcription factor that plays a role in gene regulation in bones leading to suppression of osteoid synthesis [32]. CIZ/NMP4 expression is enhanced after RANKL treatment promoting migration of B16 melanoma cell [33]. Recently, denosumab was reported to improve relapse free survival when compared with placebo in an updated analysis of the ABCSG-18 trial indicating a probable anti-tumour effect [34]. Pre-clinical model of experimental metastases and anecdotal clinical observations demonstrated that anti-CTLA-4 and anti-RANKL antibodies

have modest anti-melanoma activities individually. However, this effect is considerably enhanced when combined together [35].

Therefore, bisphosphonates and anti-RANKL antibodies may be able to delay or inhibit the development of BMs from MM. This concept can be taken as a rationale to investigate these agents in patients with MM prior to development of BMs.

New agents targeting BMs have been developed. Radium-223 dichloride, a first-in-class alpha emitter improves survival of patients with castration-resistant prostate cancer and BMs and is currently being investigated in breast cancer and other solid tumors [36,37].

The recent developments in BRAF and MEK targeted therapy (vemurafenib, dabrafenib, and trametinib) and checkpoint inhibitor immunotherapy (ipilimumab, pembrolizumab, and nivolumab) for metastatic MM have led to modest but encouraging improvement in outcome [38]. Such longer survival may well be associated with increased risk of BMs and SREs and therefore greater need for bone specific treatments. In addition, there is evidence that earlier (adjuvant) use of ipilimumab improves recurrence free survival for patients with completely resected high risk stage III melanoma [39]. However, the effects of these therapies on the development, progression and complications of MBD is not defined. Studying the effects of new therapies on MBD is encouraged of which the results can be compared against our findings which represent an earlier therapeutic era.

5. Conclusions

Our findings show that BMs occurs in 4.1% of patients with all stages MM and in 17.2% of patients with metastatic disease. Two thirds of patients with BMs experience one or more SRE indicating a significant morbidity burden. Generally, these patients have a dismal survival and hypercalcaemia in particular is a terminal event. Early use of available bone modifying agents should be considered for these patients with the opportunity to be included in future studies investigating novel agents targeting BMs.

Declaration of interest

JEB has served on advisory boards for Novartis and Amgen.
Other authors declare no conflict of interest.

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