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# Tumour-induced osteomalacia: 18 months of 2-weekly burosumab treatment

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## Summary

Tumour-induced osteomalacia (TIO) is due to an overproduction of fibroblast growth factor 23 (FGF23) by mesenchymal tumours, causing hypophosphatemia, osteomalacia and muscle weakness. TIO is usually cured by tumour resection, but neoplasms may be unidentifiable and unresectable or the patient may refuse surgery. In these cases, medical treatment with oral phosphate and calcitriol is mandatory, but it is not fully effective and it is associated with low compliance. Burosumab, a human MAB against FGF23 employed to treat X-linked hypophosphatemia (XLH), has recently been approved for TIO in the USA. Maximum burosumab dose in XLH is 90 mg administered for 2 weeks; there are no data on clinical efficacy and safety of this dose in TIO. We reported the case of a 73 years old male with multiple non-traumatic fractures, low bone mineral density, pain and reduced independence of activities of daily living. Biochemical evaluation showed hypophosphatemia, high alkaline phosphatase (ALP) and C-terminal telopeptide (CTX) and normal albumin-corrected total calcium and parathyroid hormone. Tubular phosphate reabsorption was low (80%), whereas C-terminal tail of FGF23 (cFGF23) was elevated. A $^{68}$Ga-DOTATOC PET was performed, identifying a lesion in the first left rib. The patient refused surgery; therefore, burosumab therapy was started. After 18 months of treatment (maximum dose: 60 mg administered for 2 weeks), plasma phosphate normalized and ALP levels improved (138 U/L). Patient clinical symptoms as well as pain severity and fatigue improved. Neither adverse events nor tumour progression was reported during follow-up except for a painless fracture of the second right rib.

## Learning points

- Our case shows efficacy and safety of burosumab treatment administered every 2 weeks in a tumour-induced osteomalacia (TIO) patient.
- After 18 months of treatment at a maximum dose of 60 mg every 2 weeks, we found plasma phosphate normalization and ALP reduction as well as improvement in clinical symptoms and fatigue.
- Neither adverse events nor tumour progression was reported during follow-up, except for a painless fracture of the second right rib.

## Background

Tumour-induced osteomalacia (TIO) is a rare paraneoplastic syndrome characterized by fibroblast growth factor 23 (FGF23) overproduction by benign mesenchymal tumours (1). FGF23 is produced by osteoblasts and is involved in phosphate metabolism. FGF23 overproduction leads to decreased plasma phosphate levels by inhibiting phosphate kidney reabsorption and by reducing intestinal phosphate absorption due to a lower 1-alpha-hydroxylase effect on 25(OH) vitamin D activation (1). Intact FGF23 (iFGF23) is cleaved by an unknown protease into inactive carboxy-terminal fragments (c-FGF23). TIO is rarely diagnosed in children who are more affected by hereditary hypophosphatemic diseases (i.e. X-linked hypophosphatemic rickets) (1, 2). In addition, few cases of

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FGF23-mediated hypophosphatemia have been described after i.v. iron administration (1). TIO is characterized by muscle weakness, bone pain and fractures. However, TIO clinical picture is often misdiagnosed, determining diagnostic delay (1, 3). Indeed, the reported average time from symptoms onset to diagnosis is 2.9 ± 2.3 years, leading to skeletal deformities and severe disability (1, 4). To date, $^{68}$Ga-DOTATATE PET displays the greatest sensitivity and specificity in localizing FGF23-secreting tumours, due to the expression of somatostatin type 2 receptors on mesenchymal neoplasms (1). In particular, $^{68}$Ga-DOTATATE PET protocol should be performed with the inclusion of upper and lower limbs. $^{18}$F- fluorodeoxyglucose PET ($^{18}$F-FDG-PET) may be employed when $^{68}$Ga-DOTATATE PET fails to localize TIO neoplasms (1). After detecting neoplastic lesions with functional imaging, precise localization should be performed using anatomical imaging including x-ray, CT or magnetic resonance (MR) (1). $^{99}$Technetium methoxyisobutylisonitrile scintigraphy (bone scintigraphy) is used for differential diagnosis and baseline assessment of TIO patients, identifying fractures missed on x-ray. TIO treatment is complete resection of the neoplasm, which is usually located in bone or soft tissue (1). When the FGF23-secreting tumour is undetectable, complete resection is not possible or patient refuses surgery; supplementation with phosphate and calcitriol is mandatory (1). However, compliance to oral phosphate supplementation is sometimes poor because of multiple daily administrations and gastrointestinal side effects, failing to raise plasma phosphate levels within reference ranges. Burosumab, a human monoclonal anti-FGF23 antibody, is an effective treatment for X-linked hypophosphatemic rickets and it has been recently approved by FDA for TIO, even though long-term efficacy and safety have been only partially explored (1, 2). In particular, this issue has been evaluated in ~30 TIO patients, whereas there are no data on the use of burosumab twice monthly in TIO. Here, we present a case of TIO with FGF23 overproduction treated for a long time with burosumab twice monthly.

## Case presentation

A 73 year-old-male presented for osteoporosis and multiple non-traumatic fractures at right femoral neck, dorsal vertebrae, ribs and pelvic bone. He presented progressively worsening limb pain and weakness since 3 years, with mobility limitation and walking impairment. His medical history included arterial hypertension, dyslipidaemia, previous prostate cancer treated with surgery and radiotherapy, cholecystectomy for lithiasis and mucinous pancreatic hyperplasia. Pharmacologic recognition showed the use of cholecalciferol (30 000 IU/monthly), valsartan, rosuvastatin, acetyl-salicylate and pantoprazole. He had never been prescribed iron oxide or iron polymaltose. He had no family history of bone metabolic disease. His BMI was 22.9 kg/m$^2$. Before our evaluation, he underwent oncological, urological, orthopaedic and neurosurgical examinations that did not reach a diagnostic definition for his symptoms. Dual-energy x-ray absorptiometry (DXA) showed low lumbar spine (LS) and femoral neck (FN) bone

**Table 1** Calcium and phosphate metabolism and biochemical evaluation before and after burosumab treatment.

| | Basal | 6 months | 12 months | 18 months | Reference range |
|---|---|---|---|---|---|
| Burosumab dose | 0 | | | | |
| mg | | 90/month | 50/2 weeks | 60/2 weeks | |
| mg/kg/day | | 1.29 | 1.43 | 1.71 | |
| Phosphate (mmol/L) | 0.36 | 0.61 | 0.7 | 0.9 | 0.8–1.5 |
| Calcium (mmol/L) | 2.45 | 2.42 | 2.35 | 2.42 | 2.12–2.62 |
| ALP (U/L) | 514 | 233 | 156 | 138 | 30–120 |
| CTX (ng/mL) | 0.864 | 0.720 | 0.938 | 0.550 | 0.115–0.748 |
| 25 (OH) vitamin D (nmol/L) | 100.3 | 38.2 | 94.6 | 66.9 | 50–250 |
| 1,25(OH)2 vitamin D (pmol/L) | 180 | 289 | 184 | 63 | 36.5–216.2 |
| Bone ALP (% UPN) | 690 | 375 | 192* | 172* | 3–20.2 µg/L<br>5.7–32.9 µg/L* |
| TmP/GFR (mmol/L) | 0.28 | 0.49 | 0.9 | 1.17 | 0.8–1.35 |
| TRP (%) | 80 | 81 | 95.6 | 97 | 85–95 |
| cFGF23 (pmol/L) | 3.73 | 1550 | 2482 | 3518 | <0.8 |
| iFGF23 (pmol/L) | – | 6.4 | 1.3 | 1.6 | 0.9–3.7 |
| 24-h urinary phosphate (mmol/day) | 25.8 | 22.6 | 16.1 | – | 12.9–41.9 |
| 24-h urinary calcium (mmol/day) | 1.6 | 2.6 | 2.8 | 3.5 | 1.2–10 |

*Reference range changed after 12 months of burosumab treatment. ALP, alkaline phosphatase; CTX, C-terminal telopeptide; cFGF23, C-terminal tail of fibroblast growth factor23; iFGF23, intact fibroblast growth factor 23; TmP/GFR, tubular maximum reabsorption of phosphate to glomerular filtration rate; TRP, tubular reabsorption of phosphate; UPN, upper normal values.

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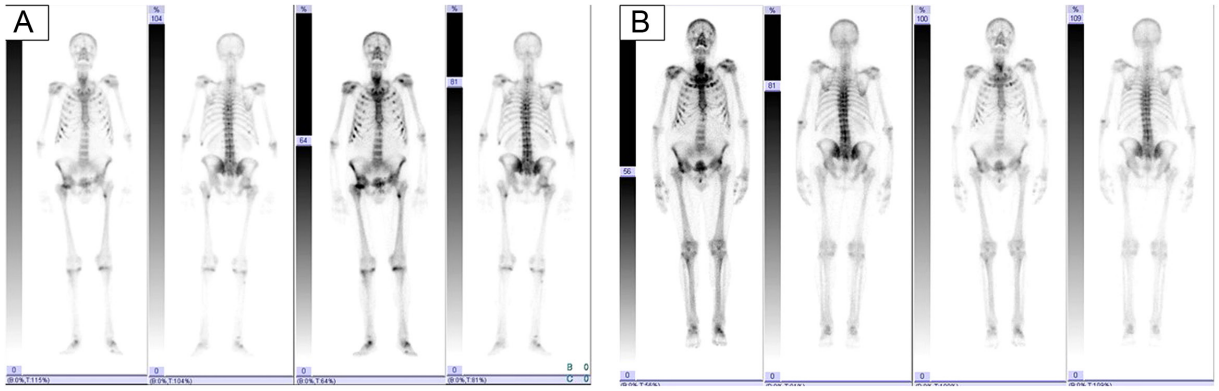


**Figure 1**
Basal $^{99}$Technetium methoxyisobutylisonitrile bone scintigraphy before (A) and after 18 months (B) of burosumab treatment.

mineral density (BMD) with T-scores of −3.1 and −4.2, respectively.

## Investigation

Initial biochemical evaluation showed hypophosphatemia (1.1 mg/dL), normal albumin-corrected total calcium, parathyroid hormone (PTH) and 25(OH) vitamin D levels, high alkaline phosphatase (ALP 514 U/L) as well as C-terminal telopeptide (CTX); 24 h urinary phosphate levels were in the upper limit of the normal range (Table 1). We found normal creatinine, low-normal 24-h urinary calcium and low phosphate tubular reabsorption (TRP: 80%), whereas c-FGF23 plasma levels were elevated (Table 1). Plasma and urinary phosphate levels were assessed with photometric UV assay; plasma and urinary calcium by a colorimetric/photometric assay, whereas chemiluminescence assays were used for 25(OH) vitamin D, PTH, CTX, iFGF23 and osteocalcin; ALP was measured by kinetic colorimetric assay, whereas c-FGF23 by immunoenzymatic assay. TRP was calculated by measuring fasting plasma phosphate and creatinine as well as second void urine phosphate and creatinine, as follows: 100 × (1 – (second void urine phosphate × plasma creatinine)/(plasma phosphate × second void urine creatinine)) (1).

Retrospective evaluation of previous biochemical analyses showed that hypophosphatemia was present since 4 years. Bone scintigraphy identified fractures at right femoral neck and small trochanter, many ribs, vertebrae, shoulders and pelvis (Fig. 1). We excluded drug-induced hypophosphatemia and other clinical causes of osteoporosis/osteomalacia such as celiac disease, mastocytosis, multiple myeloma, hyperthyroidism, hypogonadism, hyponatremia, GH deficiency and liver disease. $^{68}$Ga-DOTATOC PET scan was performed, identifying a lesion at the first left rib as possible cause of TIO (SUV max 4.5) (Fig. 2). This lesion was confirmed by $^{18}$F-FDG-PET (SUV max 8) (Fig. 3). Contrast-enhanced CT identified the specific site of the tumour and a surgeon confirmed the possibility of surgical resection. However, the patient refused surgery.

## Treatment

Therapy with oral phosphate supplementation at starting doses of 1.8 g up to 3.6 g/day in multiple daily administrations and calcitriol (1.5 µg/day) was started. However, treatment failed to normalize plasma phosphate values (1.9 mg/day after 2 months) and the patient demonstrated poor compliance. Therefore, burosumab

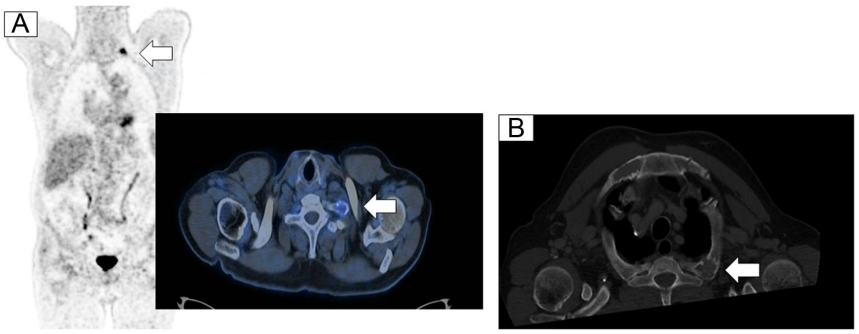


**Figure 2**
$^{18}$F-FDG-based PET/CT scan (A) identifying a lesion in the first left rib as cause of TIO (SUV max 8) and thoracic CT scan (B), confirming the lesion at the first left rib. FDG, fluorodeoxyglucose.

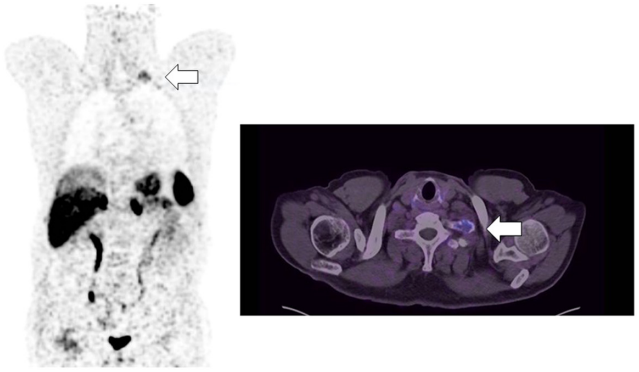

**Figure 3**
68Ga-DOTATOC-based PET/CT scan, identifying a lesion in the first left rib as cause of TIO (SUV max 4.5).

therapy was started (initial dose 0.3 mg/kg, increasing by 0.2 mg every 28 days), after discontinuing phosphate and calcitriol supplementation for 2 weeks, while maintaining cholecalciferol treatment. Basal biochemical evaluation is summarized in Table 1.

## Outcome and follow-up

After 6 months of therapy, maximal burosumab dose (90 mg/28 days) was reached obtaining an increase but not normalization in plasma phosphate (1.9 mg/dL) as well as ALP levels (233 U/L) (Table 1). Therefore, after 10 months of treatment, burosumab dosage was increased to 60 mg administered for 2 weeks. After 18 months, biochemical evaluation showed plasma phosphate normalization and further ALP reduction (138 U/L) (Table 1). Plasma phosphate, 1,25(OH)$_2$ vitamin D and bone ALP levels during burosumab treatment are summarized in Table 1 and Fig. 4.

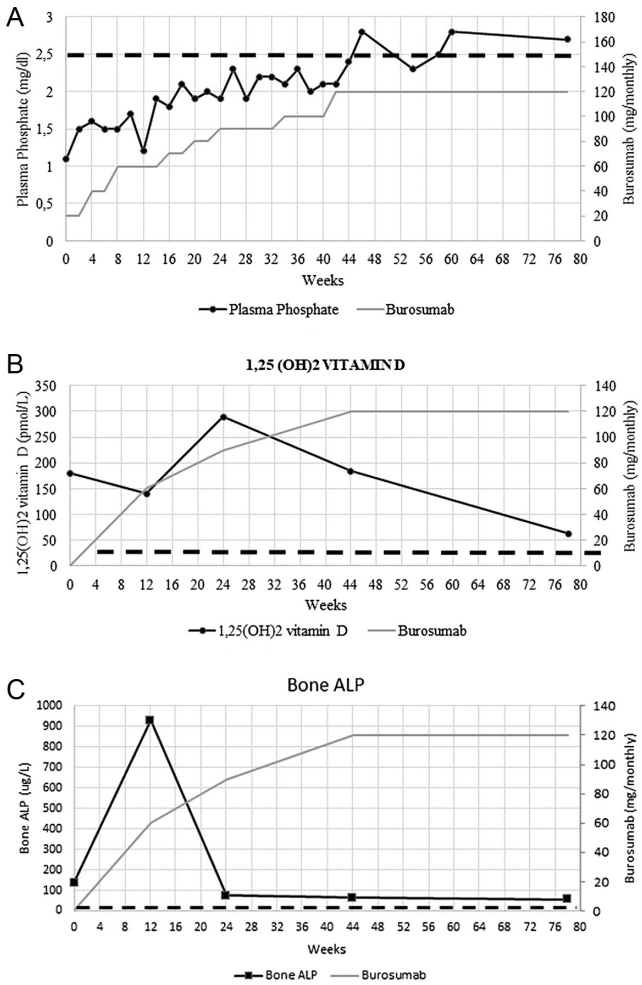


**Figure 4**
Plasma phosphate (A), 1,25(OH)2 vitamin D (B) and bone phosphatase alkaline (BALP) (C) levels during burosumab treatment. The dotted line indicates the lower normal reference range for plasma phosphate, 1,25 (OH)2 and BALP.

**Table 2** Clinical characteristics of patients treated with burosumab as reported in literature. Data are presented as mean± S.D. or as *n* (%).

| Reference | Sex, M/F | Age, years | Caucasian | BMI, Kg/m2 | Tumour localization | Treatment before burosumab | | Hypophosphatemia duration before burosumab, years |
|---|---|---|---|---|---|---|---|---|
| | | | | | | Phosphate | Calcitriol | |
| (4) | 8/6 | 56.9 ±10.3 | 12 (86%) | 33.88 ± 7.5 | 6 (43%) | 13 (93%) | 14 (100%) | 13.7 ± 13 |
| (5) | 6/7 | 60.5 ± 10.8 | 0 | Ht (cm): 151.45 ± 0.43 Wt (kg): 61.38 ± 13.02 | 7 (53.8%) | 12 (92.3%) | 13 (100%) | 10 ± 5 |
| (6) | 1/0 | 58 | 0 | 25.4 | 1 (100%) | 1 (100%) | 1 (100%) | 15 |
| (8) | 0/1 | 52 | 1 (100%) | – | 1 (100%) | 1 (100%) | – | – |
| (7) | 0/1 | 45 | – | 19.5 | 0 | 0 | 0 | – |
| Our case | 1/0 | 74 | 1 (100%) | 22.9 | 1 (100%) | 1 (100%) | 1 (100%) | 4 |

Ht, height; Wt, weight.

**Table 3** Basal biochemical evaluation of patients treated with burosumab reported in literature. Data are presented as mean ± S.D.

| Reference | P, mmol/L | iFGF 23, pg/mL | cFG23, pmol/L | 25(OH) vitamin D, nmol/L* | 1,25-$(OH)_2$ vitamin D, pmol/L | BALP, µg/L | PTH, pmol/L | TmP/GFR, mmol/L | ALP, U/L | CTX, ng/mL |
|---|---|---|---|---|---|---|---|---|---|---|
| (4) | 0.5 ± 0.47 | 15.9± 3.6 | - | 76.9 ± 29 | 68 ± 23 | 42.66 ± 5.35 | 9 ± 1.5 | 0.29 ± 0.14 | - | - |
| NR | | <3.8 | | | 42–169 | <30 | 1.9–7 | | | |
| (5) | 0.52 ± 0.16 | 39 ± 63.9 | | 66.9 ± 32.9 | 54 ± 28.49 | 36.21 ± 21.7 | 11.9 ± 4.8 | 0.37 ± 0.14 | 424.7 ± 184 | 0.6 ± 0.57 |
| NR | | <1.1 | | | 48–144 | | 1.1–6.9 | | 115–459 | |
| (6) | 0.71 | 2.1 | | 35.9 | 105.6 | 10.4 | 4 | 0.57 | 157 | - |
| NR | | <1.1 | | | 48–144 | 3.7–20.9 | 0.9–4.1 | | 106–322 | |
| (8) | 0.52 | - | - | - | 72 | - | - | - | - | - |
| NR | | | | | 44.9–179.7 | | | | | |
| (7) | 0.61 | 24.1 | | 50 | 32.2 | 36.7 | 8 | 0.51 | - | NTX: 31.5 nmol/BCE L |
| NR | | 0.61–2.6 | | | 44.9–149.8 | 2.9–14.5 | 0.9–8.4 | | | 7.5–16.5 |
| Our case | 0.35 | | 3.73 | 100 | 180 | 138 | 5.4 | 0.28 | 514 | 0.864 |
| NR | | | <0.8 | | 36–216 | 3–20.2 | 1.3–9.3 | | <120 | 0.115–0.748 |

*Normal values >75 ng/mL.
ALP, alkaline phosphatase; BALP, bone alkaline phosphatase; cFGF23, C-terminal tail of fibroblast growth factor 23; CTX, C-terminal telopeptide; iFGF23, intact fibroblast growth factor 23; NR, normal range; NTX, N-terminal telopeptide; P, plasma phopshate; PTH, parathyroid hormone; TmP/GFR, tubular maximum reabsorption of phosphate to glomerular filtration rate.

During burosumab treatment, patient's pain severity and interference with daily living activities, assessed by the Brief Pain Inventory (BPI) questionnaire, improved, as well as fatigue, assessed by the Brief Fatigue Inventory (BFI) questionnaire, and patient-reported physical and mental health outcome, evaluated by the 12-item Short Form Health Survey (SF-12) questionnaire. Sit-to-stand test and 6-min walking test also improved (from 14.83 s and 372 min to 11.08 s and 430 min, respectively), indicating improvement in physical performance. Neither adverse events nor tumour progression was reported during treatment. However, a new fracture in the second right rib was detected by $^{68}$Ga-DOTATOC-CT performed after 6 months of therapy, but at that time, plasma phosphate levels were still lower than normal. DXA performed after 18 months showed BMD improvement (LS T-score = 1.4 ; FN T-score = −1.6).

## Discussion

Our experience supports the efficacy and safety of burosumab administrated twice monthly in a TIO patient followed-up for 18 months. Clinical and biochemical characteristics of TIO patients under burosumab treatment described in the literature are presented in Table 2 and Table 3. Burosumab has been administered twice monthly in paediatric individuals with X-linked hypophosphatemia (XLH) (9). Carpenter *et al.* carried out an open-label phase II trial in 52 XLH children comparing burosumab administration schedules every 2 or 4 weeks. They found a greater decrease in rickets severity by Thacher score, a radiographic scoring system for rickets, in the group with the 2 weeks schedule as compared to the group with the 4 weeks schedule, even though the difference was not statistically significant (9). Similarly, plasma phosphate levels were more stable within the 2 weeks as compared to the 4 weeks schedule (9). In keeping with these results, subsequent paediatric studies used a burosumab regimen of 0.8 mg/kg every 2 weeks with the possibility of titrating up to 1.2 mg/kg every 2 weeks, to a maximum of 90 mg every 2 weeks (9). Our clinical report is the first describing the use of a twice-monthly schedule administration in an adult TIO patient, supporting burosumab safety and efficacy. Burosumab treatment led to higher plasma phosphate levels than those obtained with oral phosphate and calcitriol supplementation, suggesting that this approach is more effective, likely because of better patient compliance to burosumab administration as compared to multiple oral phosphate and calcitriol daily administrations. Miyaoka *et al.* compared burosumab to conventional therapy for a

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**Table 4** Adverse events reported during burosumab treatment.

| | Jan de beur *et al.* (4) | Imanishi *et al.* (5) | Our case | Total |
|---|---|---|---|---|
| Patients, *n* | 14 | 13 | 1 | 28 |
| Adverse events, *n* (%) | | | | |
| Site injection pain | 3 (21.4%) | – | – | 3 (10.7%) |
| Site injection hypersensitivity | 2 (14.3%) | 5 (38.5%) | – | 7 (25%) |
| Hyperphosphatemia | 2 (14.3%) | – | – | 2 (7.1%) |
| Ectopic mineralization | 3 (21.4%) | – | – | 3 (10.7%) |
| Restless leg syndrome | 2 (14.3%) | – | – | 2 (7.1%) |
| Arthralgia | 8 (57.1%) | 2 (15.4%) | – | 10 (35.7%) |
| Upper respiratory tract infection | 7 (50%) | – | – | 7 (25%) |
| Cough | 6 (42.9%) | – | – | 6 (21.4%) |
| Muscle pain | 4 (28.6%) | 2 (15.4%) | – | 6 (21.4%) |
| Nasopharyngitis | 4 (28.6%) | 8 (61.5%) | – | 12 (42.9%) |
| Urinary tract infections | 4 (28.6%) | 2 (15.4%) | – | 6 (21.4%) |
| Falls | 4 (28.6%) | 3 (23.1%) | – | 7 (25%) |
| Asthenia | – | 3 (23.1%) | – | 3 (10.7%) |
| Headache | 0 | 3 (23.1%) | – | 3 (10.7%) |
| Cataract | – | 2 (15.4%) | – | 2 (7.1%) |
| Constipation | – | 2 (15.4%) | – | 2 (7.1%) |
| Contusion | – | 2 (15.4%) | – | 2 (7.1%) |
| Herpes Zoster | – | 2 (15.4%) | – | 2 (7.1%) |
| Large intestine polyp | – | 2 (15.4%) | – | 2 (7.1%) |
| Nausea–dizziness | – | 2 (15.4%) | – | 2 (7.1%) |
| Septic shock | – | 2 (15.4%) | – | 2 (7.1%) |
| Tooth fracture | – | 2 (15.4%) | – | 2 (7.1%) |
| Renal lithiasis | – | 1 (7.7%) | – | 1 (3.6%) |
| New fracture | – | – | 1 (100%) | 1 (3.6%) |

recurrent TIO case, showing that oral phosphate/calcitriol supplementation did not prevent a decrease in BMD and did not normalize plasma phosphate levels, whereas burosumab normalized plasma phosphate and improved BMD after 6 months (6). In the present case report, burosumab normalized plasma phosphate, in line with other evidence (4, 5). In our report, the 90 mg monthly administration of burosumab failed to normalize plasma phosphate levels. It should be emphasized that plasma phosphate levels in our patient were lower than the average previously reported values (4, 5, 6, 7, 8), probably because of a greater FGF23 production or a longer disease duration. Our data suggest that a twice-monthly schedule may be used when maximal dosage of burosumab (90 mg/4 weeks) does not normalize plasma phosphate levels. In addition, our patient was older than patients of other studies (73vs ~60 years old) likely because of a longer diagnostic delay (4, 5). Indeed, TIO was misdiagnosed in our patient by different health care professionals, confirming that this condition often remains misdiagnosed (1). The diagnostic delay may be related to non-specific symptoms and to the small tumour size (1). The diagnostic delay leads to physical deterioration and increases the risk of clinical complications such as pain, fractures and low muscle strength, contributing to psychological impairment and depression for chronic pain and disability (1, 10). Even though there is limited literature describing the specific relationship between TIO and depression, the general relationship between chronic pain and depression is well documented (10). A 50-year-old African American female without history of psychiatric disease attempted suicide for severe bone pain due to TIO (10). Patient self-reported physical and mental outcome, severity and impact of cancer-related fatigue and pain questionnaire scores improved during burosumab treatment, in line with previous studies (4, 5). Sit-to-stand test and 6-min walking test documented an improved physical performance. In particular, physical improvement was evident as early as 3 months, despite the lack in plasma phosphate normalization, suggesting that even a slight improvement in plasma phosphate plays a role in improving patients' performance status. In two phase II open-label TIO trials, Burosumab determined an increase in bone markers and in 1,25(OH)2 vitamin D in the early phase after administration, followed by gradual decrease (4, 5). This trend was observed also in our patient. Burosumab has an acceptable safety profile and most of the adverse events reported in literature were mild to moderate and generally related to the underlying disease (4, 5) (Table 4). Our patient did not develop any adverse event during burosumab treatment except for

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a new fracture in the second rib after 6 months. At that time, his plasma phosphate levels were below the normal range, not allowing us to establish whether the new fracture was due to the use of the drug or to persisting hypophosphatemia. In Jan de Beur's study, six patients presented tumour progression, although this event was not related to burosumab use to the underlying neoplasm. In addition, five of them had already experienced disease progression before starting treatment (4). In Imanishi's study, one patient discontinued treatment because of tumour progression, whereas there were no reports of tumour progression in the remaining 12 participants (5). However, the authors neither defined tumour progression nor specified how progression was detected. The anti-FGF23 MAB improves clinical symptoms associated with neoplasia but does not have antiproliferative activity and its use does not protect against the risk of tumour progression. However, further studies on this topic are needed. Finally, a gradual increase in cFGF23 levels was observed during burosumab treatment despite iFGF23 levels normalization and plasma phosphate improvement over time. Indeed, immunological interference in immunoassays may cause false-positive or -negative results. The very high cFGF23 levels recorded during burosumab treatment may be due to a possible detection of the drug by the employed assay. However, the reason for increased cFGF23 levels during treatment deserves further studies.

**Declaration of interest**

Ludovica Aliberti, Irene Gagliardi, Margherita Pontrelli, Maria Chiara Zatelli and Maria Rosaria Ambrosio have no conflict of interest.

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**Patient consent**

Written informed consent for publication of his clinical details and/or clinical images was obtained from the patient.

**Author contribution statement**

LA and MP performed the study. LA and IG wrote the paper. MRA designed the study, performed the research and interpreted the data and critically revised the manuscript. MCZ critically revised the paper. All the authors provided final approval of this version to be published and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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