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Original Research

RANKL inhibition for giant cell lesions of the jaw: A retrospective cohort analysis

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KEYWORDS
Giant cell lesions of the jaw (GCLJ);
Denosumab;
RANKL

Abstract ***Background:*** In all giant-cell-rich lesions (GCRL) occurring in bone, a common underlying excessive RANKL expression is held responsible for the osteolytic activity. Apart from giant cell tumour of bone (GCTB), systematic outcome analysis of RANKL inhibition in other GCRL is unavailable. The aim of this study is to assess the efficacy and safety of a 1-year denosumab protocol in giant cell lesions of the jaw (GCLJ).
Methods: A retrospective cohort study was conducted compromising patients treated with a 1-year protocol of monthly subcutaneously administered 120 mg denosumab. Objective tumour response based on histology and imaging was used to calculate objective tumour response rate, progression-free survival (PFS) and time to progression. Type, severity and frequency of adverse events were recorded in a standardised way to assess safety.
Results: Twenty patients, predominantly female (90%), were included. Fifty-five per cent of lesions were located in the mandible; most classified as aggressive lesions (90%). Thirty-five per cent (7/20) of cases were either recurrent after prior treatment or progressive, while on other drug treatment. Objective tumour response rate was 100% after 12 months of treatment. Median PFS was 50.4 months (95% CI 38.0–62.8) with a cumulative PFS rate of 22.6% (95% CI 1.8–43.4) at 5 years follow-up. Median time to progression was 38.4 months (95% CI 26.0–50.8). Treatment was well tolerated, and none of the patients had to interrupt therapy for toxicity.
Conclusion: High-dose denosumab is effective and safe in achieving a complete response in GCLJ within 12 months. The high long-term relapse rate after treatment cessation is the main obstacle for denosumab to become standard treatment for GCLJ.

1. Introduction

Giant cell lesion of the jaw (GCLJ) is a rare benign osteolytic tumour with unknown aetiology [1]. It most commonly presents as asymptomatic and indolent non-aggressive lesion. Nevertheless, it may also occur as the aggressive counterpart which can be locally destructive, accompanied by dental root resorption and displacement, cortical bone destruction, and extension into soft tissues [2,3].

Traditional management of GCLJ is surgical, but this may lead to considerable morbidity depending on the size and location of the lesion. Especially for aggressive lesions, there is a high recurrence rate of up to 72% after enucleation [2,4]. A more radical approach with en-bloc resection provides a longer disease-free survival [5], at the expense of long-term functional or cosmetic sequelae and potential need for reconstructive procedures. Alternative treatments with systemic agents, such as calcitonin [6], interferon [7], or local administration of corticosteroid injections [8] have been successful in avoiding mutilating surgery. Unfortunately, none qualifies as optimal systemic treatment because of either associated toxicity or long duration of treatment [6].

Within the spectrum of giant-cell-rich tumours, GCLJ shows histomorphologically considerable overlap with giant cell tumour of bone (GCTB) [9]. Both lesions consist of mononuclear spindle-shaped cells and polygonal stromal cells expressing receptor-activator-of-nuclear-factor-kB-ligand (RANKL). These are randomly distributed among characteristic RANK-positive multinucleated osteoclast-like bone resorbing giant cells originating from the myeloid lineage [10–12]. Distinctly, GCLJs are characterized by gain-of-function mutations in *KRAS*, *FGFR1* or *TRPV4* [13], rather than the recurrent point mutations in *H3F3A* common to GCTB [14].

GCTB is currently treated with denosumab, a fully human monoclonal antibody against RANKL, which drives differentiation, survival, and activation of osteoclasts resulting in bone resorption. Clinical trials using denosumab in GCTB found that treatment resulted in a marked reduction or elimination of giant cells. This raises the question whether inhibition of RANKL can durably prevent the osteolytic activity of other tumours within the spectrum of giant-cell-rich lesions (GCRL). The aim of this study was to perform a retrospective analysis on the short-term and long-term efficacy and safety in a cohort of patients diagnosed with GCLJ and treated with a standardised protocol of one-year denosumab administration within a collaborative network in the Netherlands.

2. Patients and methods

2.1. Patient selection

A cohort of patients, diagnosed with a primary or recurrent GCLJ and treated with denosumab, was retrospectively identified from the GCLJ database of the Amsterdam University Medical Center. Only patients

Table 1
Internationally accepted grading system for behaviour based on clinical and radiological characteristics [4,7].

	Aggressive	Non-aggressive
Major criteria	Lesions ≥ 5 cm in size or those recurrent after prior treatment	<5 cm and no prior treatment
Minor criteria	≥3 of the following criteria: rapid growth, root resorption, tooth displacement, cortical bone thinning, cortical bone perforation	<3 of the following criteria: rapid growth, root resorption, tooth displacement, cortical bone thinning, cortical bone perforation

Aggressive lesions are defined as lesions with 1 major criterion or those exhibiting three or more of the minor criteria.

treated according to the protocol described below from 2012 onwards were selected.

The diagnosis of GCLJ was histologically confirmed by an experienced bone pathologist. In all cases, hyperparathyroidism was excluded. Subjects with an underlying syndrome linked to GCLJ were excluded. Patients had an Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1 or 2. All lesions were graded into aggressive or non-aggressive by the internationally accepted grading system [4,7] (Table 1).

Retrospective data collection was obtained using a standardised form. The study was assessed and found exempt from formal approvement by the Institutional Review Board of the Amsterdam UMC as based on national law [no. W21_006#21.008]. The study was performed in compliance with the Declaration of Helsinki.

2.2. Treatment protocol

All patients were treated according to a standardised 1-year denosumab protocol. This treatment protocol was offered to adult and skeletally mature patients (16 years and older) with a diagnosis of GCLJ and indication for primarily non-surgical treatment. This included lesions that were classified as aggressive, recurrent after prior treatment, progressive while on other drug treatment or where surgery would lead to considerable morbidity. The patients received subcutaneous injections of denosumab 120 mg (Xgeva, Amgen Inc., Thousand Oaks, CA, USA) as primary treatment every 4 weeks, with additional loading doses on days 8 and 15 in the first month of treatment. Treatment was discontinued after 1 year. All patients were instructed to take standard daily supplements of calcium 500 mg and vitamin D 400 IU. No other additional treatment for GCLJ was allowed. Absolute contraindications for treatment were active dental or jaw problems necessitating oral surgery; non-healed dental oral surgery; and pregnancy. Birth control was required in fertile women.

During treatment, physical examination and response evaluation by computer tomography was performed at baseline, at least once during treatment (preferably after 6 months), and after 12 months. Blood samples assessing calcium homoeostasis were taken at baseline, repeated at least three monthly thereafter, or more frequently if necessary.

Disease status during follow-up was assessed clinically and radiologically. As there are no general guidelines, follow-up was at the discretion of the treating physician. Mandatory follow-up included physical examination and CT scan between 6 and 12 months after end of treatment and at 12–24 monthly intervals thereafter; follow-up continued for 5 years or until disease progression. Radiological examination was performed if progressive disease was suspected. Histological confirmation was advised.

Table 2
Response criteria for Histology and Radiology.

Response	Definition histology	Definition radiology (modified ICDS) [15]
CR	Complete elimination of all giant cells	An increase in CT density (Δ% average HU) by ≥ 250% and no increase in volume compared with baseline
PR	>50% and <100% elimination of all giant cells	A decrease in size (Δ% volume) ≥ 10% or an increase in CT density (Δ% average HU) by > 15% compared with baseline
SD	No elimination of giant cells	Does not meet the criteria for CR, PR or PD
PD	No elimination of giant cells	An increase in size (Δ% volume) ≥ 10% compared to baseline and does not meet criteria for PR using CT density

Abbreviations: CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, HU = Hounsfield unit, CT = computer tomography, ICDS = inverse Choi density/size.

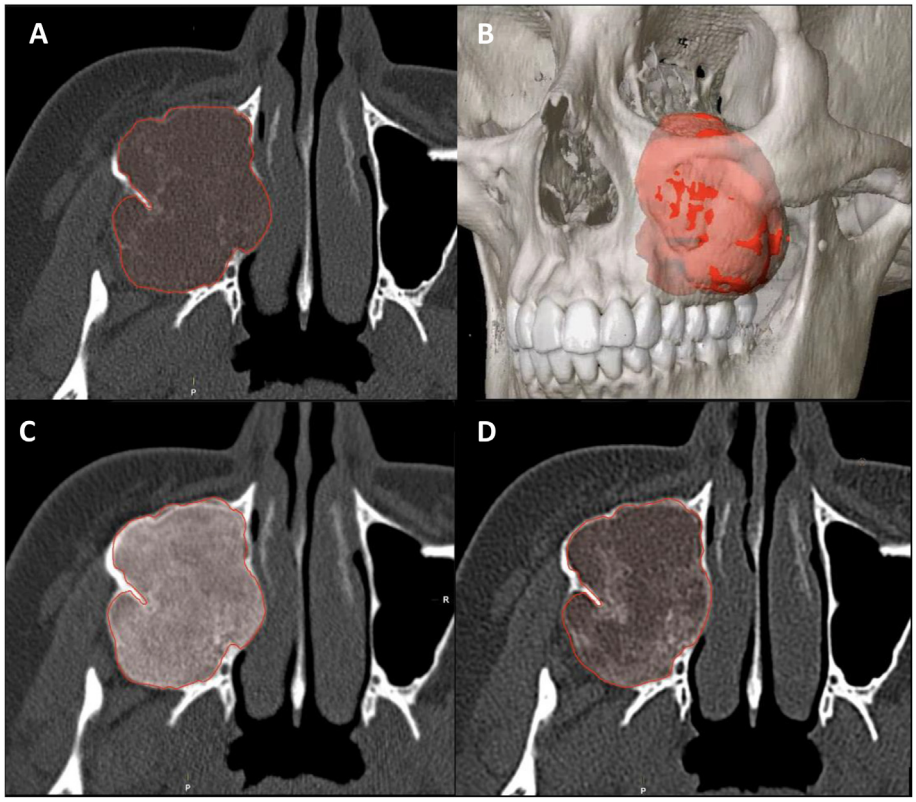

Fig. 1. **Workflow of image analysis**. After fusion of all consecutive scans, the tumour was delineated on every individual axial slide of baseline CT scan (A), enabling the creation of a 3D segmented model and calculating total volume and average Hounsfield units (HU). (B) The complete segmented tumour model was copied, projected and accordingly adjusted in every individual axial slide of consecutive fused scans. This way a similar analysis was facilitated in all scans, giving tumour volumes and average HU of annotated lesions during and after treatment. Changes in CT density and volumes were observed between, e.g., the first scan during treatment (C) and at progression after treatment discontinuation (D).

2.3. Outcome assessment

The primary end-point was efficacy, defined by objective tumour response rate (ORR: proportion of patients who achieved complete response at the end of treatment), progression-free survival (PFS: the time from the day of start of treatment until radiologic progression or histological confirmation of recurrent disease or death by any cause) and the cumulative progression-free rate (PFR) after an interval of 3 and 5 years of follow-up. Time to progression (TTP) was defined as the time from stop of treatment until radiological progression or histological confirmation of recurrent disease.

Objective tumour response was summarised based on histology or imaging in case histopathology was not available (Table 2). Response on imaging was assessed in respect to density and volume of the lesion using the inverse Choi density/size (ICDS) criteria with two modifications [15]. The first modification was made to the ICDS criteria for complete response, as denosumab leads to complete ossification but never complete disappearance of target lesions with (extra-osseous) expansion. The second modification was the use of the target lesion volume instead of the sum of longest diameter. Brainlab software (Origin/iPlan Cranial, Brainlab AG, Munich, Germany) was used for this analysis (Fig. 1). For each case, all CT scans available for analysis were fused using the fusion tool from this software. Lesion borders were manually traced in every axial slide of the baseline CT scan enabling the creation of a three-dimensional reconstruction of the lesion. The lesion under study was copied, projected and adjusted accordingly in all consecutive fused scans. Density on CT scans was expressed in Hounsfield units (HU). For each time point, volume of the annotated lesion and average HU (including standard deviation) were used for comparison and statistical analysis.

Our secondary end-point was safety, defined by type, severity, and frequency of adverse events recorded, graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 enabling a classification into grade 1 (mild), grade 2 (moderate), grade 3 (severe), or grade 4 (life-threatening).

2.4. Statistical analysis

Statistical analysis was descriptive in nature, and only summary statistics are presented. PFS was estimated

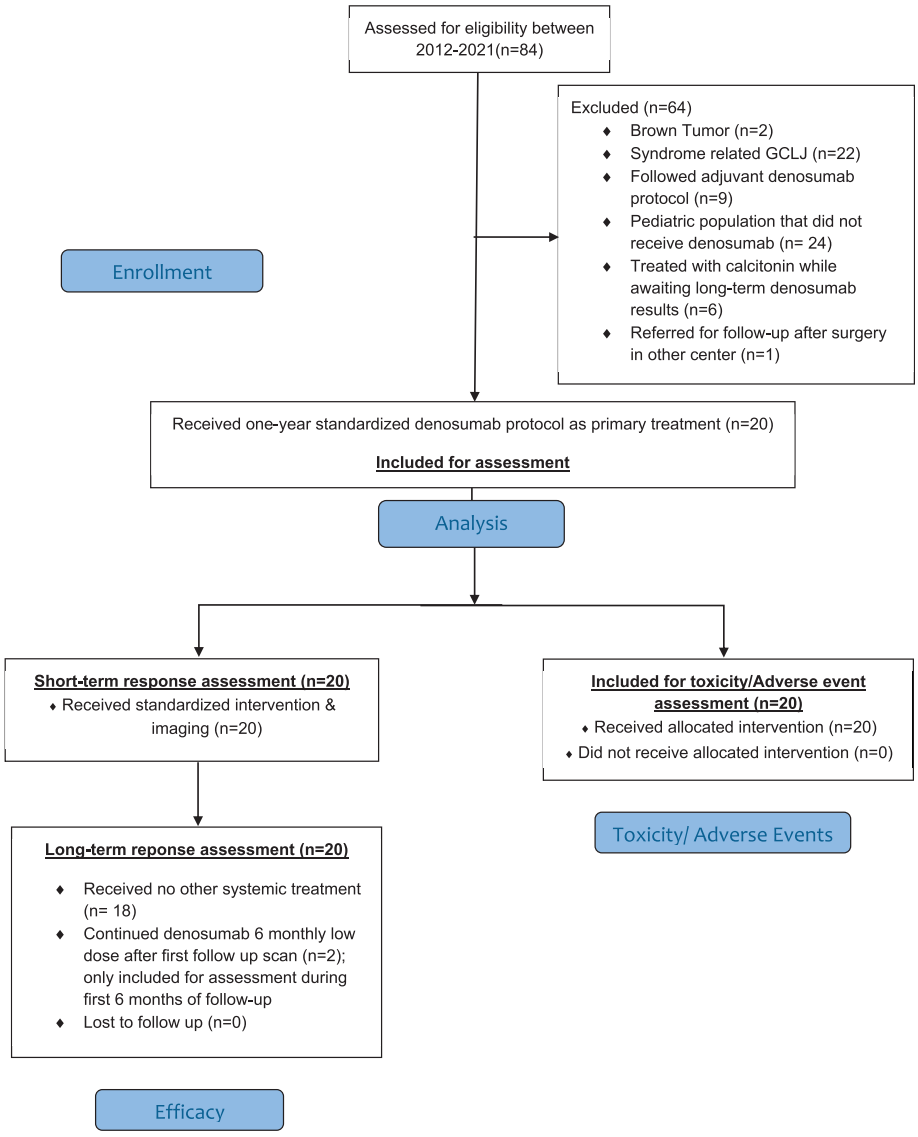

Fig. 2. Consort flow diagram.

with Kaplan–Meyer method, including 95% confidence interval (CI). Progression, indicating failure for PFS, was defined as loss of patients' best response compared to baseline. Patients without progression were censored at the time of last follow-up. Univariable Cox proportional regression models were used to investigate effects of age, aggressivity, and volume on PFS. All statistical analyses were performed using SPSS version 28.0 (IBM, Chicago, IL).

3. Results

3.1. Population

A total of 20 patients, seen in our outpatient clinic with a GCLJ between January 2012 and December 2021, fulfilled the inclusion criteria (Fig. 2). All 20 patients underwent and completed the standardised 1-year denosumab protocol. Baseline patient demographics and clinicopathologic characteristics are shown in Table 3. There was a predominance of females (n = 18; 90%); the mean age at diagnosis was 36.0 (±15.1) years. Most lesions were located in the mandible (55%), and mean volume of lesions at baseline CT scan was 11.37 (±10.43) cm^3 (Fig. 3). Most lesions were not priorly treated (n = 13; 65%), one lesion remained progressive under other systemic treatment (calcitonin and interferon) and six lesions were recurrent GCLJ after prior treatment. These treatments were either surgery (n = 5) or a combination of surgery and systemic treatment with calcitonin and interferon (n = 1). Eighteen lesions (90%) were classified as aggressive lesions.

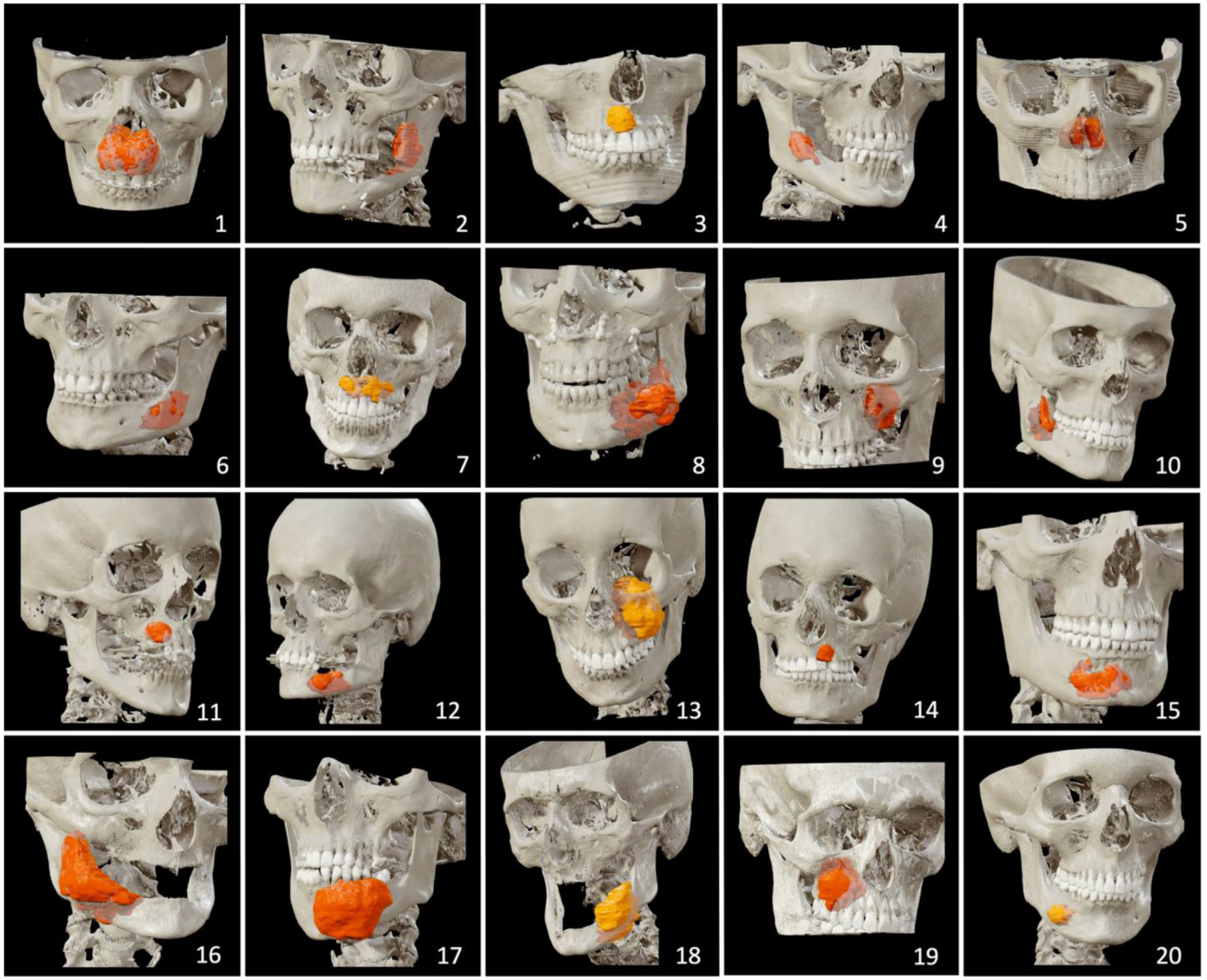

Fig. 3. **Localisation of the tumour in the patients**. The numbers in this figure correspond to the patient number in Table 2.

Table 3
Patient characteristics at baseline.

Patient	Gender	Age (yrs)	ECOG PS	Disease	Previous Treatment	Location	Sublocation	Aggressivity	Volume (cm3)
1	F	24	0	NR	Calcitonin & PEG-Interferon	Maxilla	Premaxilla	A	31.68
2	F	52	0	R	Surgery	Mandible	Ramus	A	4.97
3	F	17	0	P	None	Maxilla	Premaxilla	A	1.17
4	F	50	0	P	None	Mandible	Ramus	NA	2.86
5	F	45	0	P	None	Maxilla	Palate	A	9.19
6	F	47	0	P	None	Mandible	Corpus	A	3.11
7	F	24	1	R	Surgery; Interferon & Calcitonin	Maxilla	Premaxilla	A	7.68
8	F	31	0	R	Surgery	Mandible	Corpus	A	22.34
9	F	43	0	P	None	Maxilla	Tuber	A	7.40
10	F	21	0	R	Surgery	Mandible	Ramus	A	5.90
11	F	67	0	P	None	Maxilla	Lateral	A	1.93
12	F	53	0	P	None	Mandible	Corpus	A	7.31
13	F	22	0	P	None	Maxilla	Lateral	A	31.56
14	F	21	0	R	Surgery	Maxilla	Premaxilla	A	0.59
15	F	36	0	P	None	Mandible	Corpus	A	4.17
16	F	36	0	P	None	Mandible	Corpus	A	24.15
17	F	25	0	R	Surgery	Mandible	Corpus	A	22.60
18	M	56	0	P	None	Mandible	Corpus	A	21.05
19	M	19	0	P	None	Maxilla	Lateral	A	16.25
20	F	21	0	P	None	Mandible	Corpus	NA	1.04

Abbreviations: M = male, F = female, ECOG PS = Eastern Cooperative Oncology Group Performance Status, R = recurrence, NR = non-responsive, P = primary, A = aggressive, NA = non-aggressive.

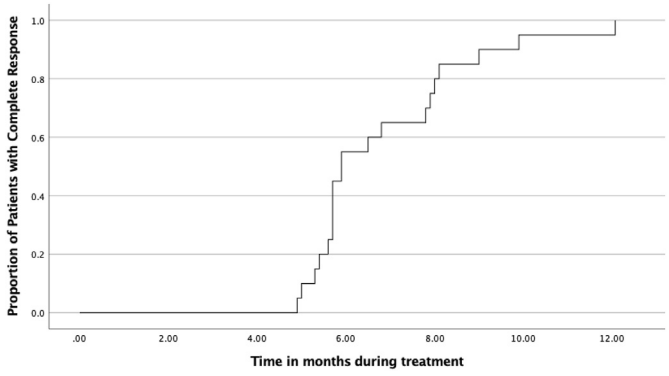

Fig. 4. Time to achieve complete response during treatment.

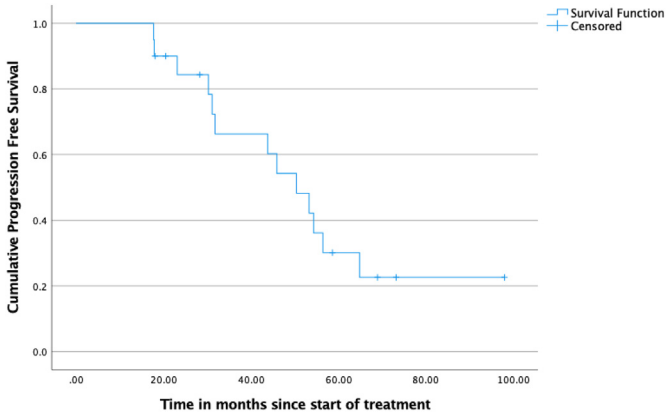

Fig. 5. Progression-free survival curve.

Table 4
Adverse events recorded.

Adverse Events	G1		G2		G3		G4	
	n	%	n	%	n	%	n	%
Fatigue	6	30	3	15	0		0	
Myalgia	6	30	0		0		0	
Arthralgia	4	20	1	5	0		0	
Bone pain	3	15	0		0		0	
Headache	2	10	1	5	0		0	
Rash acneiform	2	10	0		0		0	
Nausea	2	10	0		0		0	
Anorexia	2	10	0		0		0	
Malaise	2	10	0		0		0	
Epistaxis	1	5	0		0		0	
Generalised muscle weakness	1	5	0		0		0	
Abdominal pain	1	5	0		0		0	
Amnesia	1	5	0		0		0	
Hyperhidrosis	1	5	0		0		0	
Arthritis	1	5	0		0		0	
Dyspepsia	1	5	0		0		0	
Constipation	0		1	5	0		0	
Paraesthesia	0		1	5	0		0	
Dizziness	0		1	5	0		0	
Hypophosphatemia	5	25	2	10	1	5	0	
Anaemia	3	15	1	5	0		0	
Metabolic: Vitamin D deficiency	2	10	5	25	0		0	
Hyperkalemia	2	10	0		0		0	
Hypocalcaemia	2	10	0		0		0	
Alanine amino transferase increase	1	5	1	5	0		0	

Abbreviations: G1 = Grade 1; G2 = Grade 2; Grade 3 = Grade 3; G4 = Grade 4.

3.2. Efficacy

The best response in all 20 patients was complete response (CR), giving an objective response rate (ORR) of 100% after 12 months of treatment. All but one patient demonstrated a CR at the first radiological response evaluation during treatment, giving a median time to CR of 6.8 months (range 4.9 months–12.1 months) based on available imaging (Fig. 4).

The median follow-up time after treatment until disease progression or last follow-up visit was 32.9 months (range 5.7 months–85.9 months). Two patients (case ID 14 and 15) were censored after the first follow-up scan, as they were included in a 6-monthly low-dose denosumab (Prolia, Amgen Inc., Thousand Oaks, CA, USA) maintenance program once the first follow-up scan was made. Both patients completed this 3-year maintenance program without disease progression; further follow-up is yet unavailable. During follow-up of the remaining 18 patients, 13 patients developed disease progression. The median PFS was 50.4 months (95% CI 38.0–62.8) (Fig. 5). The cumulative PFS rate was 54.2% (95% CI 30.5–77.9) at 3 years and 22.6% (95% CI 1.8–43.4) at 5-year follow-up. The median TTP was 38.4 months (95% CI 26.0–50.8) after end of treatment.

Univariate Cox regression analysis demonstrated that none of the selected variables were statistically significant for improved PFS. A multivariate analysis was not performed.

3.3. Toxicity

Treatment was well tolerated (Table 4). Eighteen patients (90%) reported at least one adverse event of any grade. Most patients reported grade 1 (G1; n = 16) or grade 2 (G2; n = 10) adverse events, while only one grade 3 (G3, hypophosphatemia) and no grade 4 (G4) toxicities were recorded. Fatigue was the most frequently reported adverse event, occurring at any grade in 45% of patients. Bone-related and muscle-related toxicities were also common, with myalgia (G1 30%), arthralgia (G1-2 25%), or bone pain (G1 15%) occurring most frequently. Laboratory investigations demonstrated mainly mild aberrations in calcium-phospate homoeostasis.

None of the adverse events led to interruption of the therapy, definite withholding, or reduction of the dose. All adverse events recovered after termination of therapy.

4. Discussion

This is the first reported systematic cohort analysis on short-term and long-term outcomes of GCRL other than GCTB treated with a standardised 1-year treatment protocol of denosumab. We found a 100% complete response rate with size stabilisation and ossification of both aggressive and indolent GCLJ within 1 year. After treatment cessation, the majority of lesions recurred within a median time of just over 3 years. This report has important limitations, such as the retrospective study design and the varying CT scan intervals among patients. The studied population size limited statistical analysis but is still unique considering the rarity of the disease. The uniform treatment protocol for all patients and quantitative systematic analysis of CT scans for outcome assessment has not been reported before in denosumab-treated non-GCTB GCRL. This is considered the main strength of this study, generating exclusive data to better understand the role of RANKL inhibition in GCRL and GCLJ in particular.

Standard treatment indications for denosumab are osteoporosis in a low-dose regimen and prevention of skeletal-related events secondary to cancer in a high-dose regimen. Regarding GCRL, denosumab has only been approved by the FDA and EMA for adults and skeletally mature adolescents diagnosed with unresectable GCTB or when surgical resection is likely to result in severe morbidity. In the first promising study of Thomas *et al.*, a monthly high-dose regimen led to a tumour response in 30 of 35 patients (86%; 95% CI 70–95) with surgically unsalvageable GCTB [16]. Subsequent larger multinational trials confirmed the efficacy

and safety of denosumab in this specific patient category [17,18]. It is not considered standard treatment, due to concerns of relapse after discontinuation of denosumab. These concerns were substantiated by histological evaluation of GCTB specimens following denosumab treatment. It demonstrated disappearance of the characteristic osteoclast-like giant cells, but latency of the neoplastic cell population harbouring the characteristic *H3F3A* driver mutation [19].

Also in non-GCTB GCRL, including aneurysmal bone cyst (ABC) and GCLJ, an underlying common downstream pathway of excessive RANKL expression by tumour stromal cells is held responsible for the aggressive osteolytic activity [11,12,20]. Solid evidence clarifying the role of RANKL inhibition in the treatment algorithm of these GCRL is still missing. The limited available data on the role of denosumab in ABC management are promising. Still, pivotal questions remain such as optimal treatment regimen and long-term outcome, with a cumulative recurrence risk of 27% (8/30) in the heterogeneous group of reported cases [21]. Regarding GCLJ, only 39 patients with non-familial GCLJ treated by denosumab have been reported in several single case reports and small case series [22–34]. The great variety of treatment protocols used prevent a generalised interpretation on efficacy. In these studies, dosing varied from 70 mg to 120 mg monthly, treatment duration ranged from 3 to 18 months and, in some cases, maintenance protocols were installed at different intervals. In 9 of the 39 patients, additional surgical intervention was applied [23,25–27,29,34]. Follow-up of the patients remains very limited. Three of the four recurrences described occurred in one of only two reports with more than 3-year follow-up [27,34]. Since most of them had much shorter follow-up than the median TTP of 38.2 months seen in our population, it indicates that the earlier reported results on recurrences should be interpreted with caution.

Based on the results of the current study, it can be concluded that denosumab is indeed very effective in the induction of response in non GCTB-GCRL such as GCLJ. This response is unfortunately not durable and the majority of patients are expected to relapse once off-treatment. Despite the low toxicity profile in this study, which is consistent with reported adverse events in larger trials [35,36], a longer exposure to the high-dose denosumab regimen as applied in our protocol to overcome recurrence is undesirable. More and serious cumulative dose-dependent adverse events potentially leading to interruption of treatment, such as osteonecrosis of the jaw or atypical femoral fractures, and rebound effects after denosumab discontinuation, such as hypercalcaemia or spontaneous vertebral fractures, are then to be expected [17,36–38]. Studies investigating alternative approaches to overcome these issues have so far only been undertaken in GCTB. A reduced dose of denosumab or less frequent administration of drug maintenance in patients with unresectable disease still needs to be prospectively investigated [39]. Another concept of limiting drug exposure by neoadjuvant denosumab followed by curettage is highly controversial due to the potentially increased risk of local recurrence compared to standard intralesional resection [21], but results still have to be confirmed in a phase III trial (JCOG1610) [40]. Until all long-term effects of these different (dosing) strategies are clear, denosumab should not be defined as standard treatment for non-GCTB GCRL. In case of GCLJ, it should now only be reserved for carefully selected and multidisciplinary discussed cases where short-term effects are imperative, such as rapid progressive lesions, or large lesions where disfiguring mutilating surgery remains a last resort after other therapies have failed. Meanwhile, further research should also focus on the clinical value of the recently discovered genetic alterations found in GCRL, both as target for precision medicine and as biomarker for predicting clinical treatment outcome.

5. Conclusion

High-dose denosumab is effective and safe in achieving a complete response in GCLJ within 12 months after treatment initiation. The significant risk of progression after treatment discontinuation justifies its use only in specifically selected cases. Alternative protocols designed to overcome progressive disease after drug discontinuation while preventing lifelong drug exposure are still under study in GCTB. Promising results might be extrapolated to the other GCRL, such as GCLJ.

Author contribution

Study concepts: WHS, HB, JL
Study design: WHS, CK, RS, HB, AL, HE, JL
Data acquisition: WHS
Quality control of data and algorithms: WHS, CK, RS
Data analysis and interpretation: WHS, CK, RS
Statistical analysis: WHS
Manuscript preparation: WHS
Manuscript editing: WHS, AL, AHGC, HB, PHB, RTJ, CK, RS, AMW, HG, JL
Manuscript review: All authors

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Conflict of interest statement

The authors declare that they have no known competing financial interests or personal relationships

that could have appeared to influence the work reported in this paper.

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