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"Regorafenib for Bone Sarcoma Treatment: A Comprehensive Systematic Review and Meta-Analysis

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KEYWORDS

Bone sarcoma, regorafenib, meta-analysis, progression-free survival, adverse events, tyrosine kinase inhibitors

ABSTRACT:

Background: Bone sarcomas are aggressive malignancies with limited treatment options in advanced stages. Regorafenib, an oral multi-kinase inhibitor, has shown potential efficacy in early-phase trials, but its overall effectiveness and safety remain unclear.

Objective: This systematic review and meta-analysis aimed to assess the clinical impact of regorafenib on survival outcomes and adverse events in patients with bone sarcomas.

Methods: A systematic search of PubMed, Web of Science, and Scopus was conducted for randomized controlled trials (RCTs) published between September 27, 2012, and April 2024. Eligible studies compared regorafenib with placebo in bone sarcoma treatment. Primary endpoints were progression-free survival (PFS), overall survival (OS), and adverse events (AEs). Meta-analyses were performed using a random-effects model, and heterogeneity was assessed via the I^2 statistic. Study quality was evaluated using the Cochrane RoB 2 tool.

Results: Five RCTs were included. Regorafenib significantly improved PFS (MD = 9.69 weeks; 95% CI: 4.54–14.84; $I^2 = 0\%$), while no significant improvement was observed in OS (MD = 0.85 weeks; 95% CI: -36.33–38.02; $I^2 = 0\%$). Common treatment-related adverse events included hand-foot skin reaction, hypertension, fatigue, and diarrhea.

Conclusion :Regorafenib significantly improves PFS in bone sarcoma but does not clearly improve OS. Adverse events are frequent but generally manageable. Further research is needed to optimize dosing, patient selection, and long-term survival benefits.

1. Introduction

Bone sarcomas account for 0.2% of cancer cases in the U.S., with approximately 3,300 new cases in 2016, increasing at 0.4% per year. They include osteosarcoma, chondrosarcoma, Ewing sarcoma, chordoma, adamantinoma, and other rare subtypes. Management strategies prioritize survival, limb function, and quality of life. Surgical resection ensures local control, while chemotherapy provides systemic control for eligible histologies. Limb-salvage surgery is increasingly favored over amputation.

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Chemotherapy in adult bone sarcoma is challenging, with variable responses across histological subtypes. Older age is correlated with poorer outcomes, and adverse effects of conventional chemotherapy—nausea, alopecia, fatigue, and infection—impact quality of life. Tyrosine kinase inhibitors (TKIs), such as regorafenib, have emerged as promising therapies due to their multi-target inhibition of angiogenic, stromal, and oncogenic kinases. Early-phase trials suggest regorafenib's potential in bone sarcoma treatment, warranting a comprehensive evaluation of its efficacy and safety.

2. Materials and Methods

2.1. Search Strategy

A systematic search of PubMed, Web of Science, and Scopus identified RCTs published from September 27, 2012, to April 2024. Search terms included: (Bone sarcoma OR Chondrosarcoma OR chordoma OR Ewing sarcoma OR osteosarcoma OR bone fibrosarcoma OR bone leiomyosarcoma OR Adamantinoma) AND (Stivarga OR regorafenib)

This review was registered with PROSPERO (ID: CRD42024526345) and adhered to PRISMA 2020 guidelines.

2.2. Eligibility Criteria

Included studies:

- Randomized controlled trials comparing regorafenib with placebo
- Full-text publications with efficacy and safety data

Excluded:

- Meta-analyses, reviews, case reports, abstracts, ongoing trials, trial protocols, letters, animal studies, or partial texts

2.3. Data Extraction and Quality Assessment

Data extracted included study characteristics, patient demographics, histology, treatment regimens, PFS, OS, and adverse events. Discrepancies were resolved by consensus or third-author adjudication. Study quality was assessed using Cochrane RoB 2.

2.4. Statistical Analysis

PFS and OS were analyzed using mean difference (MD), and AEs were assessed using odds ratios (OR). Heterogeneity was measured with I^2 and categorized as low (<25%), moderate (25–75%), or high (>75%). Random-effects meta-analysis was applied. Subgroup analyses were conducted by histology. Analyses were performed in R v4.3.1.

3. Results

3.1. Study Selection

From 400 records, 5 RCTs met inclusion criteria (Phase II, 2019–2024). Reasons for exclusion included duplication, lack of full text, and absence of control group.

3.2. Study Characteristics

Study	Year	Phase	Design	Condition	Country	Sample Size	M/F	Median Age	Outcomes
Davis et al.	2019	2	RCT, DBPC	Osteosarcoma	USA	42	20/22	37	PFS, OS, ORR
Duffaud et al.	2019	2	RCT, DBPC	Osteosarcoma	France	43	24/14	33	PFS, OS, AEs
Duffaud et al.	2021	2	RCT, DBPC	Chondrosarcoma	France	41	25/15	-	PFS, OS, AEs
Le Cesne et al.	2023	2	RCT, DBPC	Chordoma	France	27	16/7	66	PFS, OS, AEs
Duffaud et	2023	2	RCT,	Ewing sarcoma	France	36	28/8	32	PFS, OS,

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al.			DBPC						AEs

3.3. Risk of Bias

Most studies had low risk of bias; two had "some concerns" due to randomization reporting.

3.4. Efficacy

3.4.1. Progression-Free Survival (PFS)

Regorafenib significantly improved PFS compared to placebo (MD = 9.69 weeks; 95% CI: 4.54–14.84; I^2 = 0%) [Figure 1].

3.4.2. Overall Survival (OS)

No significant OS improvement was observed (MD = 0.85 weeks; 95% CI: -36.33–38.02; I^2 = 0%) [Figure 2].

3.5. Safety

Common adverse events included:

AE	OR	95% CI	I^2
Hand-foot skin reaction	9.30	3.59–24.07	0%
Hypertension	4.00	1.61–9.94	0%
Diarrhea	2.77	1.28–6.01	0%

Grade ≥3 AEs included hypertension, hand-foot reaction, diarrhea, and fatigue. Dose reductions were common, suggesting 160 mg/day may be excessive for long-term use. No grade 5 events or deaths were reported.

4. Discussion

This meta-analysis demonstrates that regorafenib significantly improves PFS in patients with bone sarcoma, consistent across histological subtypes. Median PFS improvements ranged from 2–3 months, clinically meaningful for patients with limited treatment options. OS remained inconclusive, potentially due to trial crossover, small sample sizes, or insufficient follow-up.

Comparatively, other TKIs such as pazopanib, sorafenib, apatinib, and cabozantinib show modest efficacy in osteosarcoma, with median PFS ranging from 3–6 months and partial response rates between 7–43%. Regorafenib compares favorably in PFS, though OS impact remains uncertain.

Adverse events are consistent with known regorafenib toxicity profiles. Hand-foot reaction, hypertension, diarrhea, and fatigue were most frequent. Dose reduction strategies (e.g., starting 80–120 mg/day) may improve long-term tolerability while maintaining efficacy. Personalized dosing and close monitoring of AEs are essential.

Limitations include small sample sizes, lack of pediatric patients, and limited long-term safety and OS data. Multi-institutional collaboration is necessary to validate findings, optimize dosing, and confirm survival benefits

5. Conclusion

Regorafenib improves PFS in bone sarcoma but does not show clear OS benefit. Adverse events are manageable but common. Dose optimization and larger trials are needed to confirm long-term efficacy and safety, especially in pediatric populations.

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