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MULTIFUNCTIONAL NANOCARRIERS BASED TYROSINE KINASE INHIBITORS FOR OSTEOSARCOMA -- CURRENT TRENDS AND FUTURE PERSPECTIVES. A NARRATIVE REVIEW

Narrative Review

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ABSTRACT

Background: Bone cancer, particularly osteosarcoma, is a highly aggressive malignancy affecting children and adolescents, often associated with poor prognosis due to resistance to conventional therapies. Recent advancements in targeted therapy, particularly the use of tyrosine kinase inhibitors (TKIs), offer new hope. However, systemic toxicity and poor tumor specificity remain significant clinical challenges.

Objective: This narrative review aims to explore the potential of nanocarrier-based delivery systems to enhance the precision and efficacy of TKIs in the treatment of bone cancer.

Main Discussion Points: The review discusses various classes of nanocarriers—including liposomes, polymeric nanoparticles, micelles, dendrimers, and metal-based systems—that have been investigated for TKI delivery. Special focus is given to stimuli-responsive and biomimetic nanocarriers, which are designed to respond to the bone tumor microenvironment, as well as to pediatric osteosarcoma applications. The role of artificial intelligence in optimizing nanocarrier design is also highlighted. Additionally, the influence of nanoparticle size on cellular uptake, as well as the promise of protein-conjugated and inorganic nanocarriers like gold and silver, are examined.

Conclusion: Nanocarriers have demonstrated significant potential in improving the therapeutic index of TKIs by enhancing tumor targeting and minimizing systemic toxicity. Despite ongoing progress, further research is essential to overcome translational barriers and ensure clinical applicability in diverse patient populations.

Keywords: Bone Cancer, Tyrosine Kinase Inhibitors, Nanocarriers, Osteosarcoma, Targeted Therapy, Nanotechnology.

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INTRODUCTION

Bone cancer, although rare and accounting for less than one percent of all global malignancies, presents a significant clinical challenge due to its aggressive nature, complex treatment requirements, and high mortality rates (1). It exists in both primary and secondary forms, each with distinct pathological characteristics and clinical implications. Primary bone cancers, such as osteosarcoma (OS), Ewing sarcoma (ES), and chondrosarcoma (CS), vary widely in their epidemiology and biological behavior—OS predominantly affects adolescents and young adults, while CS is more common in the elderly population (2,3). In contrast, secondary or metastatic bone cancers arise from the spread of malignancies originating in organs such as the breast, lung, or prostate, often signifying an advanced stage of disease progression (4). The heterogeneity of bone cancers, both in origin and manifestation, continues to hinder early diagnosis, accurate prognosis, and the formulation of standardized treatment strategies (5). Historically, bone cancer treatment has relied on a triad of surgery, chemotherapy, and radiotherapy, with advancements including limb-salvage surgical techniques and chemotherapeutic agents such as methotrexate and doxorubicin improving clinical outcomes (6). The emergence of refined radiotherapeutic approaches like intensity-modulated radiotherapy (IMRT) and proton beam therapy has also enabled more precise tumor targeting with reduced damage to surrounding tissues. However, these conventional treatments remain plagued by limitations including significant toxicity, recurrence, and therapeutic resistance, particularly in tumors such as chondrosarcomas which exhibit marked radio resistance (7,8). Furthermore, the often nonspecific and subtle early symptoms of bone cancer contribute to delayed diagnosis, diminishing the effectiveness of interventions, especially in cases involving metastasis or recurrence (9).

In response to these challenges, contemporary oncologic research has turned towards targeted therapies and nanotechnology-based drug delivery systems. Tyrosine kinase inhibitors (TKIs) have emerged as a promising therapeutic class, capable of interfering with dysregulated oncogenic pathways involving receptors such as VEGFR, EGFR, and PDGFR that are central to tumor growth, angiogenesis, and survival (10-12). However, TKIs are frequently limited by poor solubility, suboptimal bioavailability, and off-target toxicities. Parallel developments in nanotechnology offer a solution to these barriers, with nanocarriers—such as liposomes, dendrimers, and polymeric nanoparticles—demonstrating potential to enhance the pharmacokinetic and pharmacodynamic profiles of anticancer drugs (13-15). The encapsulation of TKIs within these carriers can improve their stability and specificity, thereby mitigating systemic toxicity and potentially enhancing their efficacy against resistant and metastatic bone cancers (16). Despite the extensive literature on nanocarrier-based cancer therapies, there remains a noticeable gap in reviews focused specifically on their application within the bone tumor microenvironment, particularly in pediatric osteosarcoma. Additionally, the exploration of next-generation delivery systems—such as biomimetic, stimuli-responsive, and AI-engineered nanocarriers—remains insufficient, despite their promise in achieving highly selective and personalized treatment outcomes. The integration of these smart nanotechnologies with targeted therapies may signify a pivotal step toward transforming current therapeutic paradigms in bone oncology. This review aims to critically examine the evolving landscape of bone cancer treatment, with a particular emphasis on the synergistic potential of TKIs and nanocarrier-mediated delivery systems. By exploring their mechanisms of action, clinical relevance, and future prospects, the objective is to underscore their potential to enhance the precision, efficacy, and tolerability of bone cancer management, while addressing the existing hurdles to their clinical translation (17-19).

THEMATIC DISCUSSION

Current Treatment Strategies

The conventional management of bone cancers has long depended on a multimodal approach combining surgery, chemotherapy, and radiotherapy. While these strategies have significantly improved outcomes in localized disease, they still face notable challenges in treating metastatic or recurrent cases. Recent developments have improved each of these modalities, yet limitations in efficacy, especially in advanced-stage disease, highlight the pressing need for innovation.

Surgery

Surgical resection remains the cornerstone for localized bone tumors such as osteosarcoma and Ewing sarcoma. The advent of limb-sparing techniques has replaced amputation in nearly 85% of eligible cases, preserving both limb function and patient quality of life.

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Reconstructive strategies using prostheses, bone grafts, and metal implants have further contributed to improved postoperative recovery (20,21). However, surgery is still restricted by anatomical challenges, especially when tumors are located near vital structures. Additionally, recurrence remains a concern, with rates ranging from 20–30% due to residual microscopic disease (22).

Chemotherapy

Chemotherapy forms the backbone of systemic treatment, particularly in high-grade and metastatic osteosarcoma and Ewing sarcoma. Agents like methotrexate, doxorubicin, cisplatin, and ifosfamide are integral in both neoadjuvant and adjuvant settings. These regimens have led to 5-year survival rates of 60–70% in localized osteosarcoma, although this drops to 20–30% in metastatic cases (23). Nonetheless, their use is marred by dose-limiting toxicities including bone marrow suppression, cardiotoxicity, and nephrotoxicity. Resistance mechanisms, such as efflux transporter overexpression and genetic mutations, further reduce efficacy (24).

Radiotherapy

Radiotherapy has a selective role in bone cancer, mainly in Ewing sarcoma or unresectable tumors. Technologies like intensity-modulated radiotherapy (IMRT) and proton beam therapy have improved the precision of delivery, sparing healthy tissues. However, certain tumors like chondrosarcomas exhibit inherent radioresistance, limiting radiotherapy's utility (25,26). Moreover, adverse outcomes like osteonecrosis and secondary malignancies particularly in younger patients remain concerns.

Challenges and the Need for Innovation

Despite advancements, traditional treatment modalities remain insufficient in addressing metastatic disease, treatment resistance, and systemic toxicity. Chemotherapy's lack of tumor specificity results in severe side effects, while surgery and radiotherapy often fail to provide curative outcomes in advanced-stage cases. These limitations underscore an urgent need for novel therapeutic strategies that offer both efficacy and safety (27-29).

Transition to Emerging Therapies

Emerging approaches such as targeted therapy and nanotechnology-based drug delivery systems show promise in overcoming current limitations. Tyrosine kinase inhibitors (TKIs) offer precision targeting of oncogenic pathways, while nanocarriers enhance drug bioavailability and specificity, reducing systemic toxicity. Their integration signifies a paradigm shift toward more personalized and effective treatments for bone cancer (30-33).

2. Challenges and Limitations

Residual Disease and Recurrence

One of the most persistent issues in bone cancer treatment is the presence of residual microscopic disease following surgery, leading to recurrence in 20–30% of patients (16,34). Metastatic progression, particularly to the lungs, remains poorly managed by current systemic therapies, with survival rates remaining alarmingly low.

Systemic Toxicity of Chemotherapy

While chemotherapy plays a critical role in treatment, its non-specific nature leads to widespread toxicities including immunosuppression, fatigue, and gastrointestinal issues. High-dose methotrexate and doxorubicin, for instance, are associated with significant cardiotoxic and nephrotoxic effects, which compromise patient quality of life and often necessitate treatment modifications (35,36).

Drug Resistance

The development of resistance through mechanisms such as P-glycoprotein overexpression and target mutations severely undermines the long-term effectiveness of chemotherapy. These adaptations are particularly problematic in recurrent or metastatic osteosarcoma, where therapeutic options are already limited (37-39).

Functional and Psychological Impairments from Surgery

Although surgery is curative for many, it can result in lasting functional impairments. Limb-sparing procedures may preserve anatomy but still lead to restricted mobility and chronic pain. Furthermore, psychological stress stemming from changes in physical appearance and reduced autonomy often necessitates comprehensive rehabilitation, which is not always adequately provided (40,41).

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Limited Efficacy in Advanced Disease

In advanced or widely metastatic bone cancers, conventional interventions frequently fail to provide meaningful clinical benefit. Chemotherapy and radiotherapy are often insufficient to control systemic disease, especially in resistant cases. Mortality remains high, highlighting the need for therapeutic strategies capable of addressing both local and distant disease progression (42,43).

The Case for Innovative Therapies

The above limitations strongly advocate for the exploration of novel therapeutic strategies that can address the shortcomings of existing treatments. Targeted therapies and nanotechnology-enabled drug delivery systems hold promise in improving specificity, minimizing toxicity, and overcoming resistance (44-46).

3. Role of Adjuvant Therapies and Their Efficacy

Laser Ablation and Photothermal Therapy

Laser ablation and photothermal therapy offer localized, minimally invasive options for tumor control. The use of nanoparticles like gold nanorods enhances the precision of these therapies, although their utility remains limited in deep-seated or metastatic lesions (47). Combining these approaches with nanocarriers could potentially improve their reach and efficacy.

Immunotherapy

Bone-modifying agents such as bisphosphonates and denosumab help reduce skeletal-related events in metastatic bone disease. Denosumab, for example, reduces the risk of pathological fractures and helps maintain bone integrity, indirectly improving quality of life (48). Although not directly cytotoxic, their integration with other therapies enhances overall treatment outcomes.

Nanocarrier-Based Drug Delivery

Nanocarriers such as liposomes and polymeric nanoparticles facilitate targeted drug delivery, improving efficacy while minimizing off-target toxicity. Liposomal doxorubicin formulations, for instance, have shown reduced cardiotoxicity compared to traditional forms (49). Targeted delivery of TKIs via functionalized nanocarriers further improves drug localization and effectiveness (50).

Future Directions in Adjuvant Therapies

Emerging strategies, including stimuli-responsive and biomimetic nanocarriers, hold potential for even more precise drug delivery. The integration of immunotherapy and nanotechnology is also being explored to enhance immune responses while limiting side effects (51).

4. Tyrosine Kinase Inhibitors (TKIs) in Cancer Therapy

Mechanisms of Action and Classification

TKIs block tyrosine kinase enzymes that drive tumor growth, angiogenesis, and resistance. These are classified into receptor (e.g., VEGFR, EGFR) and non-receptor kinases (e.g., SRC, ABL), and work by disrupting key signaling pathways like RAS/MAPK and PI3K/AKT (29,30).

FDA Approved TKIs and Their Uses

Several TKIs approved for other malignancies have shown promise in bone cancers. Imatinib, sorafenib, and cabozantinib target pathways implicated in tumor proliferation and angiogenesis, and have been studied in various sarcomas with encouraging results (51).

Integration of TKIs with Conventional Therapies

TKIs can potentiate the effects of chemotherapy and radiotherapy. For example, sorafenib improves doxorubicin efficacy, while pazopanib enhances radiotherapy sensitivity by normalizing tumor vasculature (32,33).

Addressing Resistance to TKIs

Resistance to TKIs arises from mutations and alternative signaling pathway activation. Second- and third-generation TKIs like ponatinib, or combination therapies involving immunotherapy, are strategies to overcome this barrier (34,52).

The Future of TKIs in Bone Cancer Therapy

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TKIs offer a route toward personalized therapy by selectively targeting molecular drivers of cancer. Ongoing research is focused on refining their use in combination regimens and integrating them with nanotechnology for enhanced delivery (53).

5. Nanocarrier-Based Drug Delivery Systems

Mechanisms of Drug Delivery

Nanocarriers utilize passive targeting via enhanced permeability and retention (EPR) and active targeting through ligand-receptor interactions to concentrate drugs at tumor sites, thereby minimizing systemic exposure (54).

Types of Nanocarriers

Liposomes, polymeric nanoparticles (PLGA, PEG), dendrimers, gold nanoparticles, and solid lipid nanoparticles (SLNs) each offer unique properties in drug encapsulation and release (39–41).

Practical Impact and Success Stories

Preclinical and clinical studies have shown liposomal doxorubicin reduces cardiotoxicity, while PLGA nanoparticles enhance sorafenib delivery. Gold nanoparticles conjugated with TKIs have demonstrated selective cytotoxicity against osteosarcoma cells (55,56).

Integration in Combination Therapies

Co-loaded nanocarriers delivering chemotherapeutics and TKIs show synergistic anti-tumor effects. These combination strategies also reduce resistance development and improve treatment durability (57).

Future Directions

Smart nanocarriers incorporating biomimetic features and real-time imaging capabilities are under development. These innovations promise enhanced targeting accuracy and personalized treatment monitoring (45).

6. Combination Therapies

TKIs and Chemotherapy

Combining TKIs with chemotherapy has shown improved tumor regression and survival. In osteosarcoma models, sorafenib combined with doxorubicin reduced tumor volume by 70% (58). Clinical trials using regorafenib with cisplatin demonstrated longer progression-free survival compared to chemotherapy alone (59).

TKIs and Radiotherapy

TKIs like pazopanib sensitize tumors to radiotherapy by enhancing oxygenation. Cabozantinib with SBRT significantly reduced tumor burden and pain in metastatic bone cancer patients, improving functional outcomes (50–52).

TKIs and Immunotherapy

Combining lenvatinib with PD-1 inhibitors like pembrolizumab has yielded high response rates in metastatic sarcomas. This synergy results from enhanced immune infiltration and modulation of the tumor microenvironment (53–54).

Case Studies and Evidence

Clinical and preclinical data support the superiority of combination therapies over monotherapies in terms of tumor control and quality of life improvements (55–60).

Smart Nano carriers for Targeted TKI Delivery in Bone Cancer

i) Surface-Modified Smart Nano carriers

These are functionalized with PEG, antibodies, or peptides for targeted delivery. They respond to internal stimuli like pH or enzymes, ensuring drug release occurs primarily within tumor tissues (57,61).

ii) Magnetic Nano carriers and AI-Driven Optimization

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Magnetic nanoparticles allow externally guided delivery. Machine learning models help predict nanoparticle biodistribution and optimize design for enhanced targeting efficiency (62-64).

7. Adverse Effects and Mitigation Strategies

Adverse Effects of TKIs

Despite their selectivity, TKIs can cause off-target effects including gastrointestinal issues, skin rashes, and cardiotoxicity. These toxicities necessitate careful dose monitoring and patient education (64,65).

Adverse Effects of Nanocarrier-Based Drug Delivery Systems

Nanocarriers can trigger immune responses and accumulate in organs, leading to potential long-term toxicities. Understanding their biodistribution remains a challenge (66).

Mitigating Adverse Effects

Mitigation strategies include proactive monitoring, controlled drug release, and personalized dosing. Liposomal doxorubicin and pH-sensitive nanoparticles are examples of safer alternatives that maintain therapeutic efficacy while reducing toxicity (67,68).

Table 1: Comprehensive Comparison of Conventional Bone Cancer Therapies

Therapy Type	Mechanism of Action	Advantages	Limitations	Key Examples	References
Surgery	Physical tumor removal; limb reconstruction.	Preserves functionality; effective for localized tumors.	High recurrence (20–30%); not for metastases; challenges near critical structures.	Limb-sparing for osteosarcoma; amputation for invasive tumors; titanium prostheses.	(58)
Chemotherapy	Cytotoxic agents targeting dividing cells systemically.	Reduces tumor size pre-surgery; eliminates residual post-surgery.	Toxicity (cardio, nephro); drug resistance; limited for metastases.	Methotrexate + doxorubicin for osteosarcoma; cisplatin regimens for Ewing sarcoma.	(59)
Radiotherapy	Ionizing radiation damages cancer DNA.	Precise targeting minimizes healthy tissue damage; suitable for inoperable tumors.	Limited for radioresistant tumors; risk of osteonecrosis, secondary malignancies.	Proton therapy for skull base chondrosarcomas; IMRT for Ewing sarcoma.	(60)

Table 2: Approved and Investigational TKIs for Bone Cancer

TKI	Primary Targets	Applications	Benefits	Challenges	References
Imatinib	PDGFR, KIT	GIST; investigational in bone cancers	High efficacy in GIST; tolerable side effects	Resistance through mutations; limited in bone cancers.	(61)

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TKI	Primary Targets	Applications	Benefits	Challenges	References
Sorafenib	VEGFR, RAF	Osteosarcoma; advanced sarcomas	Reduces vasculature; synergistic with chemo	Drug resistance; common side effects (fatigue, hypertension).	(62)
Cabozantinib	VEGFR, MET, AXL	Metastatic bone cancers; solid tumors	Reduces skeletal events; durable responses	Fatigue, hypertension, hepatotoxicity; high cost.	(63)
Lenvatinib	VEGFR, FGFR	Osteosarcoma; metastatic sarcomas	Synergy in combination therapies; immune reactivation	High cost; risk of proteinuria, GI toxicity.	(64)
Pazopanib	VEGFR, PDGFR	Radiosensitizer in osteosarcoma	Enhances radiotherapy; durable metastatic responses	Radioresistance in hypoxic tumors; cardiotoxicity.	(65)

Table 3: Types and Functions of Nanocarriers in Bone Cancer Treatment

Nanocarrier Type	Features	Mechanism of Action	Applications	Advantages	Challenges	References
Liposomes	Lipid bilayer; encapsulates various drugs	Passive targeting via EPR; protects drugs	Liposomal doxorubicin for sarcoma therapy	Reduced toxicity; improved stability	Limited scalability; rapid MPS clearance	(66)
Polymeric NPs	Biodegradable polymers; tunable release	Controlled, sustained release; multi-drug delivery	Sorafenib-loaded PLGA in osteosarcoma models	High biocompatibility; versatile drug loading	Manufacturing complexity; off-target accumulation	(67)
Gold NPs	Functionalized gold core	Active targeting; imaging and photothermal use	Dasatinib delivery; imaging during surgery	Dual therapy-diagnostics role; precise targeting	Potential toxicity; high production costs	(68)
Dendrimers	Branched polymeric structures	Multimodal delivery; high payload capacity	Chemotherapeutics and siRNA for osteosarcoma	High efficiency; gene and drug versatility	Immune activation; challenging synthesis	(69)

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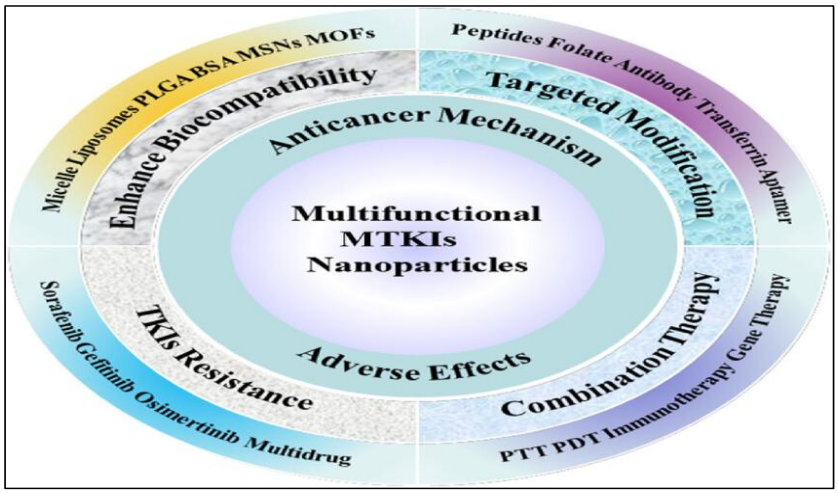
Table 4: Outcomes of Combination Therapies for Bone Cancer

Combination Therapy	Target Pathway/Mechanism	Key Results	Clinical/Preclinical Studies	References
Sorafenib + Doxorubicin	VEGFR inhibition + DNA damage in cancer cells.	70% tumor reduction; enhanced apoptosis and reduced angiogenesis.	Preclinical: Mouse models of osteosarcoma.	(70)
Lenvatinib + Pembrolizumab	VEGFR inhibition + immune checkpoint blockade.	Objective response rate of 47%; prolonged progression-free survival.	Phase II trial in metastatic sarcomas.	(71)
Cabozantinib + Radiotherapy	VEGFR and MET inhibition + radiosensitization.	Significant reduction in bone metastases; improved pain management and functional outcomes.	Clinical case studies in patients with bone metastases from prostate and breast cancer.	(72)
Pazopanib + Immune Checkpoint	VEGFR normalization + enhanced T-cell infiltration.	Reduced tumor burden; increased immune activation in bone cancer models.	Preclinical evidence supports potential for combination therapies in metastatic settings.	(73)



Pictorial representation of different therapeutic aspects of multiple tyrosine kinase inhibitors

Figure 1 Pictorial Representation of Different Therapeutic Aspects of Multiple Tyrosine Kinase Inhibitors

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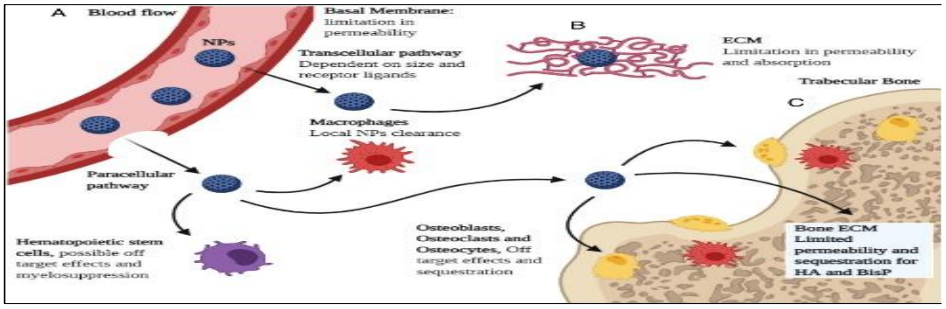
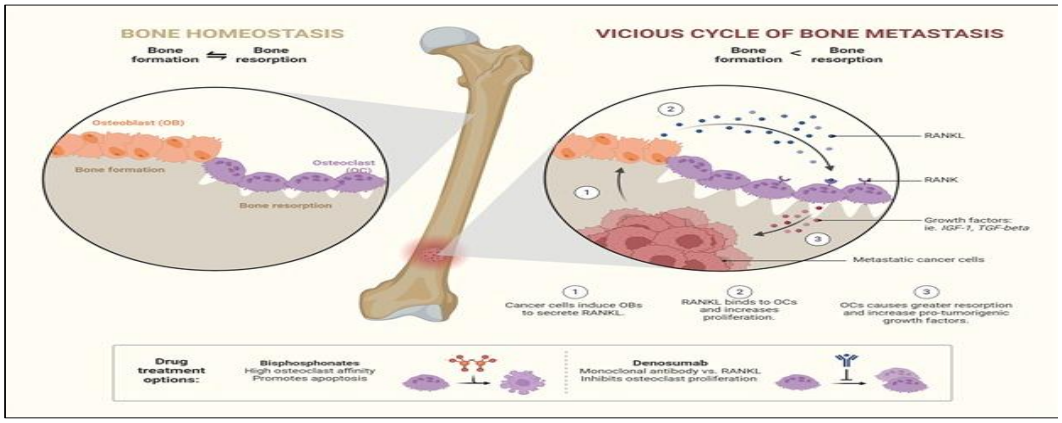


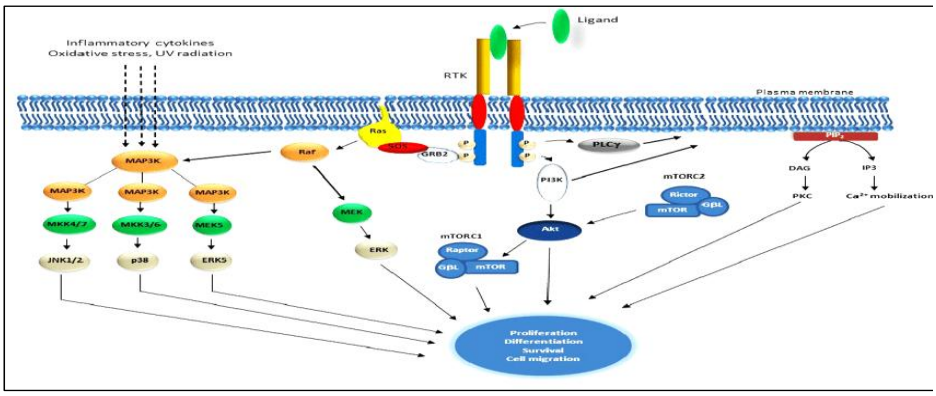
Pictorial representation of Morphology of bone, parts of bone include osteoclast, osteoblast and osteocytes showing blood flow toward bone

Figure 2 Pictorial Representation of Morphology of Bone, Parts of Bone Include Osteoclast and Osteocytes Showing Blood Flow Toward Bone



Bone homeostasis and the vicious cycle of bone metastasis: potential therapeutic interventions

Figure 3 Bone Hemostasis and the Vicious Cycle of Bone Metestsiss: Potential Therapeutic Interventions



Pictorial representation of mechanism followed by Tyrosine Kinase Inhibitors using different pathways. (TKIs) in Bone Cancer Treatment.

Figure 4 Pictorial Representation of Mechanism Followed by Tyrosine Kinase Inhibitors Using Different Pathways (TKLs) in Bone Cancer Treatments

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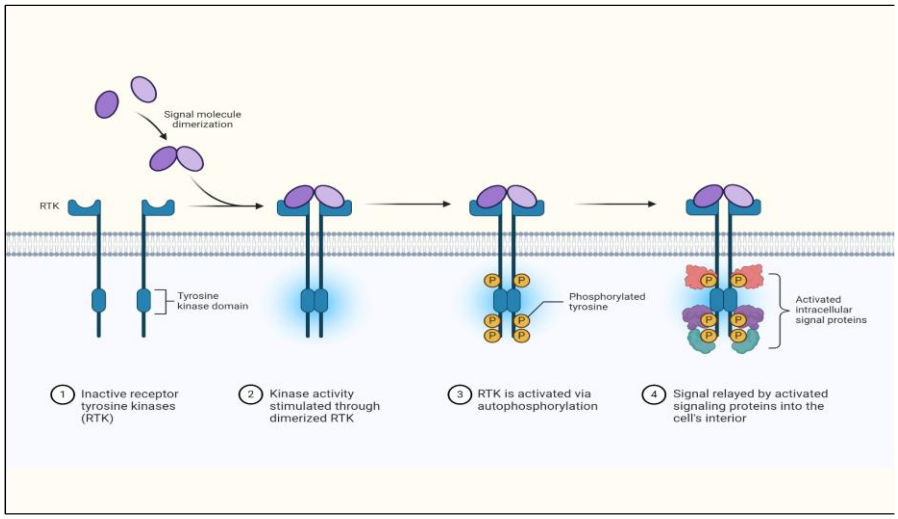

Mechanism of receptor tyrosine kinase (RTK) activation and intracellular signaling cascade

Figure 5 Mechanism of receptor Tyrosine Kinase (RTH) Activation and Intercellular Signaling Cascade

CRITICAL ANALYSIS AND LIMITATIONS

The current body of literature on bone cancer treatment, though extensive and growing, exhibits notable limitations that must be acknowledged to guide future research and clinical application. A primary limitation lies in the design of many of the included studies. Several investigations, particularly those exploring targeted therapies and nanocarrier-based systems, are based on small preclinical or early-phase clinical trials with limited sample sizes. This constrains the statistical power and reliability of the results, making it difficult to draw robust conclusions. Moreover, the lack of large-scale randomized controlled trials (RCTs) is evident, especially in emerging areas such as the integration of TKIs with immunotherapy or nanotechnology-based drug delivery. The absence of RCTs raises concerns regarding the internal validity and reproducibility of reported outcomes (61–63). Methodological bias further complicates the interpretation of existing findings. Selection bias is commonly seen, with many studies enrolling patients with favorable baseline characteristics or excluding those with comorbidities, which skews the applicability of the results. Performance bias is also prevalent due to insufficient blinding, particularly in open-label trials where subjective outcomes such as quality of life or pain reduction may be influenced by patient or physician expectations. Additionally, there is limited uniformity in treatment protocols and dosing regimens across studies, making direct comparisons difficult and potentially confounding pooled analyses (64,65). Publication bias is another critical issue. Positive results, especially those showing promising therapeutic effects of TKIs or nanocarrier-based systems, are more likely to be published, whereas studies with negative or inconclusive findings remain underreported. This selective reporting creates a skewed understanding of the actual efficacy and safety profiles of these therapies. Consequently, systematic reviews or meta-analyses may overestimate the benefits of these interventions and underestimate potential risks or limitations (67,68).

Another significant limitation arises from variability in the measurement of treatment outcomes. Different studies utilize a range of endpoints—ranging from radiological tumor shrinkage and progression-free survival to biochemical markers or subjective patient-reported outcomes—without standardized metrics. Such variability reduces the comparability of results and complicates the synthesis of evidence across trials. Furthermore, inconsistency in follow-up durations undermines the ability to assess long-term efficacy, toxicity, and recurrence rates, especially in chronic or relapsing disease scenarios like osteosarcoma (69). Generalizability of findings also remains constrained. Much of the current literature is derived from highly specialized or geographically limited institutions, and predominantly involves younger, healthier patient cohorts. This introduces concerns regarding the external validity of study outcomes, particularly in elderly populations, patients with poor performance status, or those from underrepresented ethnic and socioeconomic groups. Pediatric bone cancers, such as Ewing sarcoma, also lack adequate age-stratified data to support uniform treatment strategies across different age groups (70). Addressing these limitations requires more rigorous, multicentric, and inclusive research designs. Future

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investigations should emphasize randomized controlled methodologies with adequate sample sizes, standardization of outcome measures, and longer follow-up periods to capture the full trajectory of treatment response and survivorship. Importantly, transparent reporting of negative results and real-world data from diverse clinical settings will be crucial for developing evidence-based, equitable, and effective treatment paradigms for bone cancer.

IMPLICATIONS AND FUTURE DIRECTIONS

The integration of precision medicine, nanotechnology, and immunotherapy into bone cancer treatment offers significant implications for clinical practice, policy development, and future research. As this review highlights, these innovations may reshape therapeutic paradigms, particularly for advanced or resistant bone cancers where current treatment strategies remain inadequate. Clinically, the application of tyrosine kinase inhibitors (TKIs) and nanocarrier-based drug delivery systems could enhance the specificity and efficacy of treatment while minimizing systemic toxicity (71). This approach may enable more personalized care plans that align treatment with tumor biology and patient-specific profiles, ultimately improving outcomes and reducing adverse effects. For example, incorporating predictive biomarkers such as VEGFR or PDGFR mutations can assist clinicians in selecting the most appropriate targeted therapy, enhancing therapeutic decision-making and patient stratification. From a policy and guideline standpoint, these emerging therapies necessitate the revision of current clinical protocols to incorporate biomarker testing, molecular profiling, and access to advanced technologies. The rapid evolution of these modalities calls for the development of standardized clinical guidelines that support their safe and effective integration into routine care. Policymakers must also consider the implications of cost, access, and scalability, especially in low- and middle-income countries where advanced treatments may remain out of reach (72,73). Addressing these disparities through subsidized programs or international collaborations could help bridge the gap in global cancer care. Despite promising developments, several critical questions remain unanswered. Long-term safety and efficacy data for many nanotechnology-based systems and TKIs in bone cancer are still limited. There is also a lack of robust evidence concerning the most effective combinations and sequences of these therapies with existing modalities such as chemotherapy or radiotherapy.

Furthermore, the tumor microenvironment in bone cancers—particularly in pediatric populations—requires deeper investigation to identify optimal targets and delivery strategies. As these therapies become more complex, understanding the biological interactions at both cellular and systemic levels becomes imperative. Future research must prioritize large-scale, multicenter randomized controlled trials that evaluate these novel therapies across diverse patient populations. Emphasis should be placed on trials with standardized endpoints, long-term follow-up, and comprehensive toxicity monitoring. In addition, real-world evidence studies will be essential in assessing how these therapies perform outside of highly controlled trial environments. Methodological improvements should also include stratification by molecular markers, use of adaptive trial designs, and incorporation of patient-reported outcomes to better capture treatment impact on quality of life. Incorporating artificial intelligence and machine learning to optimize nanocarrier design and treatment personalization may also serve as a key innovation in future studies. Ultimately, the convergence of technological innovation and personalized medicine holds substantial promise for transforming the management of bone cancer. To fully realize this potential, continued interdisciplinary collaboration, equitable resource allocation, and patient-centered research approaches are essential. The future of bone cancer therapy lies not only in the discovery of more effective treatments but also in ensuring that these advances reach all patients, regardless of geography or socioeconomic status.

CONCLUSION

The integration of tyrosine kinase inhibitors (TKIs) and nanocarrier-based drug delivery systems marks a transformative advancement in the treatment of bone cancer, addressing several longstanding limitations of conventional therapies such as systemic toxicity, therapeutic resistance, and non-specific targeting. By enabling precise disruption of oncogenic pathways and improving drug localization, these modalities enhance therapeutic efficacy while preserving patient quality of life. The current evidence, although promising, is largely based on preclinical studies and early-phase clinical trials, and while the mechanistic rationale is robust, broader validation through high-quality, long-term, and multicenter research is essential. For clinicians, these developments underscore the importance of molecular profiling and individualized treatment strategies, while researchers are encouraged to refine delivery platforms and optimize combination regimens. Moving forward, greater emphasis must be placed on overcoming barriers to clinical translation, including cost, regulatory hurdles, and equitable global access. Future studies should aim to identify predictive biomarkers, expand real-world data, and include diverse populations to ensure these innovations benefit all patients facing this aggressive disease.

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AUTHOR CONTRIBUTIONS

Author	Contribution
Muhammad Mubashir Rasheed*	Substantial Contribution to study design, analysis, acquisition of Data Manuscript Writing Has given Final Approval of the version to be published
Javeria Javed	Substantial Contribution to study design, acquisition and interpretation of Data Critical Review and Manuscript Writing Has given Final Approval of the version to be published
Nabgha Zafar	Substantial Contribution to acquisition and interpretation of Data Has given Final Approval of the version to be published
Irum Asif	Contributed to Data Collection and Analysis Has given Final Approval of the version to be published
Riad Azzam Kouzeiha	Contributed to Data Collection and Analysis Has given Final Approval of the version to be published
Muhammad Muzzamil Rasheed	Substantial Contribution to study design and Data Analysis Has given Final Approval of the version to be published
Ifra Ghori	Contributed to study concept and Data collection Has given Final Approval of the version to be published

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