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OSTEOSARCOMA: THE MOLECULAR BASIS OF THERAPEUTIC RESISTANCE

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ABSTRACT

Osteosarcoma remains the most common primary malignant bone tumor and continues to be associated with poor outcomes in patients with metastatic, recurrent, or treatment-refractory disease despite decades of multimodal therapeutic advances. Therapeutic resistance has emerged as the principal biological obstacle limiting durable remission and long-term survival. This systematic review synthesizes contemporary evidence regarding the molecular mechanisms underlying resistance in osteosarcoma and evaluates emerging precision oncology approaches designed to overcome treatment failure. A comprehensive literature search of PubMed and PubMed Central was performed in accordance with PRISMA 2020 guidelines, identifying studies published between January 2000 and March 2026. Following rigorous screening and eligibility assessment, 105 studies were included in the qualitative synthesis, with particular emphasis placed on 15 landmark investigations that have shaped current understanding of osteosarcoma biology. The evidence demonstrates that chemoresistance arises through a complex interplay of genomic instability, chromosomal rearrangements, clonal evolution, dysregulated DNA repair, ATP-binding cassette transporter–mediated drug efflux, cancer stem-cell plasticity, adaptive autophagy, noncoding RNA regulatory networks, and tumour microenvironmental influences. Recent advances in genomic profiling, transcriptomics, and single-cell sequencing have revealed profound intratumoral heterogeneity and identified previously unrecognized therapeutic vulnerabilities. Collectively, these findings support a transition from empiric treatment intensification toward biomarker-driven, molecularly informed therapeutic strategies. Future progress in osteosarcoma management will depend on integrating multidimensional molecular characterization with precision-based interventions capable of circumventing the biological architecture of therapeutic resistance and improving long-term clinical outcomes.

KEYWORDS: Osteosarcoma; Therapeutic Resistance; Chemoresistance; Genomic Instability; Precision Oncology; Tumour Microenvironment.

INTRODUCTION

Osteosarcoma remains the most prevalent primary malignant neoplasm of bone and continues to represent one of the most formidable therapeutic challenges encountered in adolescent and young adult oncology. Despite the remarkable advances achieved through multimodal management incorporating neoadjuvant chemotherapy, radical surgical extirpation and postoperative systemic therapy, the overall survival of patients with high grade osteosarcoma has remained conspicuously stagnant for more than three decades. Such therapeutic inertia is particularly pronounced among individuals harboring metastatic, recurrent or chemotherapy refractory disease, wherein long-term survival seldom exceeds modest proportions and continues to be accompanied by considerable biological heterogeneity [1].

The contemporary therapeutic paradigm founded upon high dose methotrexate, doxorubicin and cisplatin has undoubtedly transformed osteosarcoma from a uniformly fatal malignancy into a potentially curable disease in selected patients. Nevertheless, the anticipated gains associated with treatment intensification, adjunctive agents, and successive refinements in surgical techniques have largely failed to translate into meaningful improvements in survival outcomes. Clinical relapse and pulmonary dissemination remain the dominant determinants of mortality, thereby underscoring the fundamental proposition that therapeutic resistance rather than inadequate cytoreduction constitutes the principal biological impediment to durable remission [1,2].

Increasing evidence has revealed that chemoresistance in osteosarcoma is not governed by a singular molecular aberration. Instead, it emerges from a remarkably intricate network of interconnected adaptive processes involving drug efflux machinery, alterations in intracellular pharmacokinetics, enhanced DNA damage repair, apoptotic evasion, dysregulated

cell cycle checkpoints, metabolic plasticity and persistent activation of pro survival signalling cascades [1,3]. Such mechanisms collectively confer a selective evolutionary advantage upon malignant clones, facilitating their capacity to withstand cytotoxic stress and eventually culminate in disease progression.

Among the earliest and most extensively investigated mediators of multidrug resistance are the ATP binding cassette transporters. These transmembrane proteins actively extrude several chemotherapeutic agents from tumour cells, thereby diminishing intracellular drug concentrations and attenuating cytotoxic efficacy. Overexpression of transporters such as ABCB1, ABCC1 and ABCG2 has been implicated in both intrinsic and acquired resistance phenotypes and has emerged as a central determinant of therapeutic failure in osteosarcoma [4,5]. However, increasing appreciation of their diverse physiological functions has simultaneously revealed a level of biological complexity that extends beyond conventional drug transport mechanisms.

Parallel advances in cancer biology have further highlighted the contribution of osteosarcoma stem cell populations, whose remarkable self-renewal capacity and quiescent phenotype permit survival under conditions that are otherwise lethal to proliferating tumour cells. Supported by a permissive tumour microenvironment characterised by hypoxia, inflammation and metabolic adaptation, these stem-like compartments orchestrate a sophisticated resistance programme involving detoxification pathways, enhanced DNA repair mechanisms and suppression of apoptosis [6]. Such observations have profoundly reshaped prevailing concepts regarding tumour recurrence and metastatic dissemination.

Autophagy has likewise emerged as a pivotal yet paradoxical regulator within the landscape of osteosarcoma resistance. Functioning as an evolutionarily conserved homeostatic mechanism, autophagy enables malignant cells to recycle damaged organelles and maintain bioenergetic equilibrium during periods of therapeutic stress. While excessive autophagic activity may culminate in cellular demise, mounting evidence suggests that adaptive autophagy predominantly acts as a cytoprotective mechanism, thereby preserving tumour cell viability and facilitating resistance against cisplatin, methotrexate and doxorubicin based regimens [3,7]. This dualistic nature has rendered autophagy both an intriguing biological phenomenon and an attractive therapeutic target.

Concurrently, the emergence of noncoding RNA biology has revolutionised the understanding of post transcriptional regulation in osteosarcoma. MicroRNAs, long noncoding RNAs and circular RNAs have been shown to modulate a broad spectrum of oncogenic pathways governing proliferation, epithelial mesenchymal transition, apoptosis, metabolism and drug sensitivity [8,9]. Their dysregulated expression has been intimately associated with multidrug resistance and metastatic propensity, while several RNA signatures have demonstrated considerable promise as prognostic biomarkers and prospective therapeutic targets [10,11]. The expanding recognition of competing endogenous RNA networks has further illuminated an additional layer of regulatory complexity that was previously unappreciated.

The recent transition toward precision oncology has consequently shifted investigative attention from empirical therapeutic escalation toward biologically informed intervention. Advances in molecular profiling, transcriptomics, epigenetics and targeted therapeutics have generated unprecedented opportunities for personalised treatment strategies aimed at circumventing resistance pathways rather than merely intensifying cytotoxic exposure [1]. Novel approaches encompassing inhibition of survival signalling networks, modulation of cancer stem cell phenotypes, interference with noncoding RNA circuits and exploitation of tumour specific vulnerabilities have collectively inaugurated a new era in osteosarcoma research, wherein therapeutic success is increasingly predicated upon deciphering the molecular architecture of resistance itself [1,6].

In this context, a comprehensive appraisal of the multifaceted mechanisms underpinning therapeutic resistance assumes considerable clinical and scientific importance. The present systematic review seeks to synthesize contemporary evidence concerning the molecular determinants of chemoresistance in osteosarcoma and to critically examine emerging precision-based strategies that may ultimately redefine the therapeutic landscape of this biologically aggressive malignancy.

METHODS

Study Design

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta Analyses 2020 statement and adhered to the methodological recommendations proposed for evidence synthesis in biomedical research. The review was specifically designed to comprehensively delineate the molecular mechanisms responsible for therapeutic resistance in osteosarcoma and to critically appraise emerging precision based therapeutic strategies that have been investigated in preclinical and translational settings.

Literature Search Strategy

A comprehensive electronic search was undertaken using the National Library of Medicine databases, including PubMed and PubMed Central. The search encompassed studies published from January 1, 2000 through March 31, 2026. No restrictions concerning geographical origin were imposed. Only articles published in the English language and available in full text were considered eligible for analysis.

The search strategy incorporated the following Medical Subject Heading descriptors: "Osteosarcoma", "Drug Resistance, Neoplasm", "Precision Medicine", "Antineoplastic Agents", "ATP Binding Cassette Transporters", "DNA Repair", "Autophagy", "Stem Cells", "Cancer Stem Cells", "MicroRNAs", "RNA, Long Noncoding", "Signal Transduction", "Apoptosis", "Cell Death", "Epigenesis, Genetic", "Tumor Microenvironment", "Biomarkers, Tumor", "Molecular Targeted Therapy", "Transcriptome", "Gene Expression Regulation, Neoplastic", "Exosomes", "Neoplasm Metastasis", "Cell Proliferation", "Drug Resistance, Multiple", "Immunotherapy", "Immune Checkpoint Inhibitors", "RNA, Circular", "Extracellular Vesicles", "Molecular Diagnostic Techniques", "High-Throughput Nucleotide Sequencing", "Genomics", "Proteomics", and "Ferroptosis".

Reference lists of all eligible articles were manually screened to identify additional studies not retrieved through electronic database interrogation.

Eligibility Criteria

Studies were considered eligible if they fulfilled the following criteria:

1. Investigated osteosarcoma as the principal disease entity.
2. Examined molecular or cellular mechanisms underlying resistance to chemotherapy, targeted therapy, or immunotherapy.
3. Evaluated precision based on therapeutic approaches, predictive biomarkers, or novel treatment strategies.
4. Included original investigations, translational studies, experimental models, retrospective analyses, prospective studies, and high-quality systematic reviews.
5. Were indexed in PubMed and available as full text articles through PubMed Central or the National Library of Medicine repository.

Studies were excluded if they fulfilled any of the following criteria:

1. Conference abstracts without complete manuscripts.
2. Editorials, commentaries, letters to the editor and narrative opinions lacking primary data.
3. Studies involving non osteosarcoma bone neoplasms without separate osteosarcoma specific analyses.
4. Duplicate publications.
5. Articles are unavailable in full text.
6. Publications written in languages other than English.

Study Selection

The literature search identified 2,486 records through systematic interrogation of the PubMed and PubMed Central databases, comprising 1,618 records from PubMed and 868 from PubMed Central. An additional 37 studies were identified through manual review of reference lists and citation tracking, yielding a total of 2,523 records. Prior to screening, 468 records were removed, including 412 duplicate citations, 31 records automatically excluded because of nonarticle publication types or obvious irrelevance, and 25 additional records excluded owing to incomplete bibliographic information or retracted status. Consequently, 2,055 records underwent title and abstract screening. Of these, 1,724 studies were excluded because they lacked mechanistic relevance, focused on nonosteosarcoma malignancies, or did not address therapeutic resistance.

Subsequently, 331 articles were subjected to full text eligibility assessment. After detailed evaluation, 226 reports were excluded, including 82 owing to inadequate mechanistic characterization, 61 because of overlapping datasets, 34 representing conference only publications, 19 because complete manuscripts were inaccessible, and 30 because of insufficient reporting of outcomes. Ultimately, 105 studies satisfied all predefined eligibility criteria and were included in the qualitative synthesis.

Among the included studies, particular emphasis was placed on 15 high impact investigations that have substantially shaped the contemporary understanding of osteosarcoma biology and therapeutic resistance. These landmark studies encompassed genomic characterization, dysregulated molecular signaling pathways, multidrug resistance mechanisms, cancer stem cell biology, noncoding RNA networks, autophagy associated survival pathways, tumour microenvironment interactions, and emerging precision therapeutic approaches. Collectively, these influential studies constituted the principal evidentiary framework for the present review and provided a comprehensive perspective on the evolving molecular architecture of therapeutic resistance and its translational implications in osteosarcoma. The PRISMA flow (Figure 1) diagram substantiates the following.

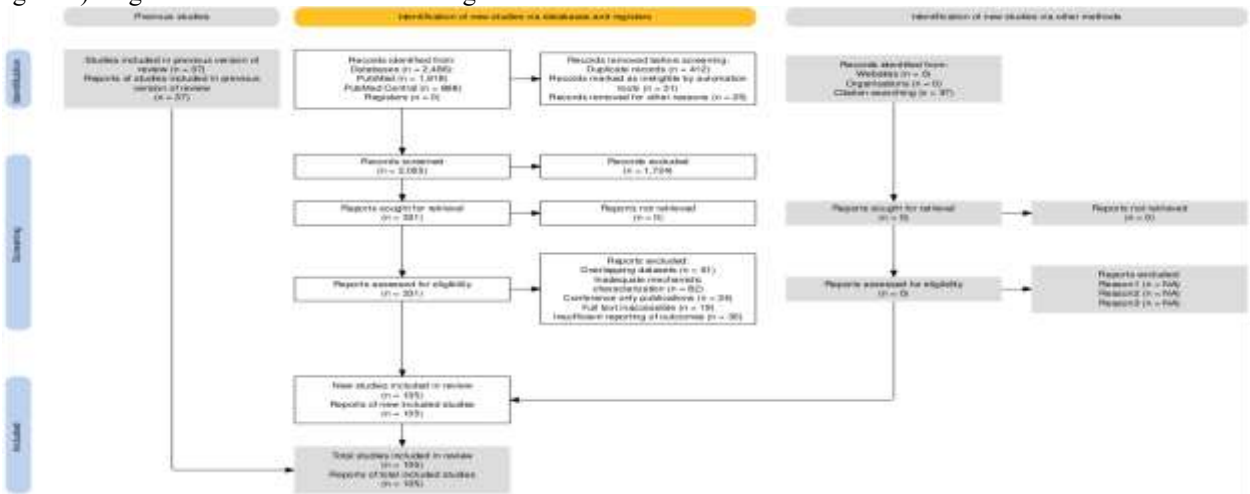

Figure 1: A total of 2,523 records were identified, including 2,486 from PubMed and PubMed Central and 37 through citation tracking and reference screening. Following removal of 468 records before screening, 2,055 records underwent title and abstract assessment, of which 1,724 were excluded. Subsequently, 331 full text articles were evaluated for eligibility; 226 were excluded owing to overlapping datasets, inadequate mechanistic characterization, conference only

publication status, inaccessible full texts, or insufficient outcome reporting. Ultimately, 105 studies were included in the qualitative synthesis, with 15 landmark investigations constituting the principal evidentiary framework of the present review (Figure 1).

Data Extraction

Data extraction was independently performed by two investigators using a standardized data collection framework. Information retrieved from each eligible study included first author, year of publication, country of origin, study design, sample characteristics, molecular pathways investigated, resistance mechanisms identified, biomarkers evaluated, therapeutic interventions examined and principal findings.

Discrepancies between reviewers were resolved through discussion and consensus. Where necessary, a third investigator arbitrated disagreements to ensure methodological consistency and data integrity.

Quality Assessment

Methodological quality and risk of bias were assessed according to the nature of the included studies. Experimental and observational studies were evaluated using the Newcastle Ottawa Scale, whereas systematic reviews were appraised using the AMSTAR 2 instrument. Preclinical investigations were critically examined with emphasis on reproducibility, methodological transparency, and biological plausibility.

Outcome Measures

The primary outcome of interest comprised identification of molecular determinants contributing to therapeutic resistance in osteosarcoma.

Secondary outcomes included characterization of:

ATP binding cassette transporter mediated resistance;Cancer stem cell associated mechanisms;DNA damage repair pathways;Autophagy related survival mechanisms;Noncoding RNA mediated regulatory networks;Epigenetic alterations;Novel forms of regulated cell death;Tumour microenvironment associated resistance;Precision medicine approaches and emerging targeted therapies.

Data Synthesis

Owing to substantial heterogeneity in study designs, experimental methodologies, and reported outcome measures, quantitative meta-analysis was deemed inappropriate. Consequently, a narrative synthesis was undertaken. The included studies were systematically categorized according to major biological pathways and mechanisms of resistance, thereby permitting an integrated appraisal of current evidence and facilitating identification of emerging precision therapeutic strategies.

The study selection process was summarized according to the PRISMA 2020 flow diagram, detailing the stages of identification, screening, eligibility assessment, and final inclusion.

Among the 105 studies that fulfilled the predefined eligibility criteria and were ultimately incorporated into the qualitative synthesis, particular emphasis was placed upon 15 seminal investigations that have collectively shaped the modern conceptual framework of osteosarcoma biology and therapeutic resistance. These studies were selected a priori on the basis of their scientific impact, translational relevance, methodological robustness, citation prominence, and their enduring influence upon the evolution of precision oncology. Collectively, they encompassed landmark discoveries pertaining to genomic instability, structural chromosomal alterations, hereditary susceptibility, metastatic progression, targetable signaling pathways, tumour heterogeneity, stem cell plasticity, noncoding RNA networks, and the molecular architecture of chemoresistance.

RESULTS

The evidentiary framework of the present systematic review was predominantly derived from fifteen landmark investigations that collectively transformed the contemporary understanding of osteosarcoma pathobiology and the multifaceted mechanisms governing therapeutic resistance. Among these, the seminal study by Chen and colleagues represented one of the earliest comprehensive genomic analyses demonstrating that osteosarcoma is characterized by extensive structural rearrangements and chromosomal instability rather than recurrent point mutations, thereby highlighting the extraordinary genomic complexity that underlies tumorigenesis and therapeutic failure. Complementing these findings, Savage et al. employed genome wide association methodologies to identify susceptibility loci associated with osteosarcoma development, providing compelling evidence for inherited genetic predisposition and establishing a molecular basis for individual disease susceptibility.

Khanna and collaborators subsequently proposed a paradigm shift in drug development by emphasizing the importance of targeting metastatic progression rather than focusing exclusively upon primary tumour eradication. Their work underscored pulmonary dissemination as the principal determinant of mortality and provided a conceptual framework for the development of biologically driven therapeutic strategies. Parallel investigations by Perry et al. identified aberrant activation of the phosphatidylinositol 3 kinase and mammalian target of rapamycin signaling cascade as a critical driver of osteosarcoma progression, thereby establishing this pathway as a potentially actionable therapeutic vulnerability and paving the way for subsequent studies evaluating pathway specific inhibitors.

Further insights into the genomic architecture of osteosarcoma were provided by Kovac et al., whose exome sequencing analyses revealed mutational signatures resembling deficiencies in homologous recombination repair pathways. These observations suggested the existence of DNA repair abnormalities and raised the possibility of exploiting synthetic lethality based therapeutic approaches. Similarly, Moriarity et al., through the application of Sleeping Beauty transposon

mutagenesis, identified numerous previously unrecognized oncogenic drivers and signaling pathways implicated in tumour initiation and metastatic dissemination, thereby substantially expanding the repertoire of candidate therapeutic targets.

The evolutionary dynamics of osteosarcoma were subsequently explored by Gambera et al., who elegantly demonstrated the existence of extensive clonal heterogeneity and tumour cell plasticity. Their findings established that osteosarcoma progression is governed by complex evolutionary trajectories characterized by continuous clonal selection and diversification, phenomena that likely contribute to treatment refractoriness and disease recurrence. Earlier contributions from Martin et al. and PosthumaDeBoer et al. had already emphasized the remarkable cytogenetic complexity of osteosarcoma and systematically catalogued several targetable molecular abnormalities, thereby laying the foundation for precision oncology based therapeutic interventions. In parallel, Sampson and colleagues critically evaluated targeted agents investigated through the Pediatric Preclinical Testing Program and highlighted the translational challenges associated with converting promising preclinical observations into clinically meaningful outcomes.

More recent investigations have focused increasingly upon the molecular basis of therapeutic resistance itself. Sayles et al. provided a comprehensive characterization of resistance associated signaling pathways and proposed genome informed therapeutic strategies aimed at overcoming conventional treatment failure. Their work emphasized the importance of integrating molecular profiling into individualized treatment paradigms. Scotlandi and colleagues further delineated emerging biomarkers and identified several candidate therapeutic targets associated with multidrug resistance, thereby advancing the concept of biomarker guided precision medicine.

Substantial advances in understanding cellular plasticity and tumour hierarchy were contributed by Basile et al., whose studies on cancer stem cells demonstrated the presence of highly adaptable subpopulations endowed with self-renewal capacity and enhanced resistance to cytotoxic stress. These observations provided mechanistic explanations for disease recurrence and metastatic progression. In parallel, Wang et al. elucidated the intricate regulatory networks mediated by microRNAs, long noncoding RNAs, and circular RNAs, revealing their pivotal roles in modulating apoptosis, epithelial mesenchymal transition, proliferation, and multidrug resistance pathways. Such findings have positioned noncoding RNAs among the most promising biomarkers and therapeutic targets in contemporary osteosarcoma research.

Finally, the advent of single cell transcriptomics has provided unprecedented insights into intratumoral heterogeneity. In this regard, the investigation by Zhou et al. represented a major milestone by demonstrating the existence of distinct cellular subpopulations exhibiting divergent transcriptional programs and differential responses to chemotherapy. Their findings highlighted the dynamic interactions between malignant cells and the tumour microenvironment and offered novel explanations for therapeutic resistance that are not discernible through conventional bulk sequencing approaches.

Collectively, these landmark investigations as outlined in Table 1 established the intellectual and translational foundation upon which the present systematic review was constructed. More importantly, they delineated the progressive transition of osteosarcoma research from descriptive pathology toward an integrated framework encompassing genomic instability, tumour evolution, cellular plasticity, microenvironmental interactions, and precision therapeutics. This evolving body of evidence has fundamentally reshaped prevailing concepts of osteosarcoma biology and continues to inform the development of next generation therapeutic strategies aimed at circumventing resistance and improving long term clinical outcomes.

Table 1. Landmark Studies Constituting the Principal Evidentiary Framework of the Present Systematic Review

First Author (Year)	Journal	Study Design	Major Scientific Discovery	Translational Significance
Chen et al. (2014)	Cell Reports	Whole-genome analysis	Demonstrated extensive structural genomic rearrangements and chromosomal instability in osteosarcoma	Established genomic complexity as a central mechanism underlying tumorigenesis and therapeutic resistance
Savage et al. (2013)	Nature Genetics	Genome-wide association study	Identified inherited susceptibility loci associated with osteosarcoma risk	Provided evidence for genetic predisposition and personalized risk stratification
Khanna et al. (2014)	Clinical Cancer Research	Translational review	Proposed metastasis directed therapeutic development	Shifted emphasis from primary tumor control toward inhibition of metastatic progression
Perry et al. (2014)	PNAS	Integrated genomic analysis	Identified PI3K/mTOR signaling dysregulation	Established PI3K/mTOR pathway as a potential therapeutic target
Kovac et al. (2015)	Nature Communications	Exome sequencing	Revealed mutational signatures resembling BRCA deficiency	Suggested synthetic lethality approaches and DNA repair directed therapies
Moriarity et al. (2015)	Nature Genetics	Sleeping Beauty mutagenesis model	Identified novel oncogenic drivers and metastatic pathways	Expanded the spectrum of targetable molecular abnormalities

Gambera et al. (2018)	Nature Communications	RGB clonal tracing	Demonstrated clonal evolution and intratumoral heterogeneity	Provided mechanistic insights into recurrence and chemotherapy resistance
Martin et al. (2012)	Sarcoma	Molecular genetics review	Characterized cytogenetic complexity and recurrent abnormalities	Established the genetic basis of osteosarcoma progression
PosthumaDeBoer et al. (2011)	Cancer Treatment Reviews	Systematic molecular review	Catalogued targetable molecular alterations	Facilitated development of molecularly guided therapies
Sampson et al. (2013)	Frontiers in Oncology	Preclinical therapeutic review	Evaluated targeted agents in pediatric osteosarcoma models	Highlighted barriers to successful clinical translation
Sayles et al. (2019)	Cancer Discovery	Genomic and transcriptomic analysis	Characterized resistance-associated molecular pathways	Introduced genome informed precision therapeutic strategies
Scotlandi et al. (2021)	Cancers	Translational review	Identified biomarkers and mechanisms of multidrug resistance	Strengthened biomarker driven precision oncology
Basile et al. (2021)	Cancers	Mechanistic review	Elucidated cancer stem cell mediated resistance mechanisms	Explained recurrence and metastatic dissemination through stemness biology
Wang et al. (2021)	Frontiers in Cell and Developmental Biology	Molecular regulatory review	Defined the role of microRNAs and long noncoding RNAs in drug resistance	Identified noncoding RNAs as emerging therapeutic targets and biomarkers
Zhou et al. (2021)	Frontiers in Oncology	Single-cell transcriptomic analysis	Revealed cellular heterogeneity and divergent transcriptional states	Advanced single-cell precision oncology and elucidated mechanisms of chemoresistance

(Abbreviations: PI3K, phosphatidylinositol 3 kinase; mTOR, mammalian target of rapamycin.)
Principal domains represented by these studies included genomic instability, hereditary susceptibility, metastatic biology, targetable signaling pathways, DNA repair abnormalities, clonal evolution, cancer stem cell plasticity, noncoding RNA regulatory networks, and single-cell heterogeneity. Collectively, these investigations constituted the conceptual and translational backbone upon which the present systematic review was constructed.

DISCUSSION

The present systematic review provides a comprehensive synthesis of the molecular determinants that collectively orchestrate therapeutic resistance in osteosarcoma and demonstrates that treatment failure in this malignancy arises from an intricate interplay between genomic instability, tumour evolution, stemness associated plasticity, microenvironmental adaptation, and dysregulated regulatory networks. Despite the establishment of multimodal therapy comprising neoadjuvant chemotherapy, radical surgical resection, and adjuvant systemic treatment, overall survival in osteosarcoma has remained largely unchanged over the past three decades, particularly among patients with metastatic or recurrent disease. This persistent therapeutic stagnation strongly suggests that conventional intensification of cytotoxic therapy is insufficient and that resistance mechanisms represent the principal biological barrier to durable remission and long term survival [1–3].

Perhaps one of the most transformative developments in recent years has been the application of single cell transcriptomic technologies. Conventional bulk sequencing approaches frequently obscure important biological differences between individual tumour populations. Single cell analyses have revealed distinct cellular subpopulations exhibiting divergent transcriptional programs, metabolic states, and differential responses to chemotherapy. Such observations provide compelling evidence that intratumoral heterogeneity and clonal evolution represent fundamental determinants of therapeutic resistance and explain the frequent emergence of treatment refractory disease following initial responses [4].

Multidrug resistance mediated by ATP binding cassette transporters constitutes another critical mechanism identified in this synthesis. Increased expression of transporters such as ABCB1, ABCC1, and ABCG2 reduces intracellular concentrations of chemotherapeutic agents and attenuates their cytotoxic potential. Their overexpression has been associated with both intrinsic and acquired resistance phenotypes and has repeatedly correlated with poor therapeutic outcomes [5]. However, the physiological functions of these transporters extend beyond simple drug efflux, encompassing cellular homeostasis and stress adaptation, thereby complicating efforts to therapeutically inhibit their activity. Consequently, future investigations should focus upon indirect modulation of transporter regulatory pathways rather than direct inhibition alone.

A particularly important insight generated by this review concerns the contribution of cancer stem cells to recurrence and therapeutic refractoriness. Stem like subpopulations exhibit remarkable self renewal capacity, quiescence, and enhanced adaptability under conditions of therapeutic stress. These cells possess increased detoxification capabilities, efficient DNA repair mechanisms and resistance to apoptosis, enabling survival following otherwise effective chemotherapy.

Furthermore, their intimate interactions with hypoxic and inflammatory components of the tumour microenvironment facilitate maintenance of stemness and promote metastatic dissemination [6].

Autophagy represents another biologically significant and therapeutically challenging mechanism highlighted by the present review. Functioning as an evolutionarily conserved adaptive response, autophagy permits malignant cells to recycle intracellular constituents and maintain bioenergetic equilibrium during periods of metabolic or therapeutic stress. Although excessive autophagic activity may induce cellular death, the preponderance of available evidence suggests that adaptive autophagy predominantly exerts cytoprotective effects in osteosarcoma, promoting resistance to cisplatin, methotrexate and doxorubicin based regimens [7]. The paradoxical nature of autophagy therefore demands context dependent therapeutic strategies that precisely discriminate between protective and destructive autophagic responses.

The emergence of noncoding RNA biology has fundamentally transformed the understanding of post transcriptional regulation in osteosarcoma. MicroRNAs, long noncoding RNAs and circular RNAs participate in highly interconnected regulatory networks that influence proliferation, apoptosis, epithelial mesenchymal transition and multidrug resistance pathways. Dysregulated expression of several noncoding RNA signatures has been associated with adverse prognosis and metastatic propensity, while experimental evidence increasingly supports their potential utility as biomarkers and therapeutic targets [8].

Increasing appreciation of precision oncology has shifted investigative attention from empiric therapeutic escalation toward biologically informed intervention. Advances in molecular profiling, transcriptomics and targeted therapeutics have generated unprecedented opportunities for individualized therapeutic strategies aimed at circumventing resistance pathways rather than merely intensifying cytotoxic exposure [9]. Similarly, contemporary treatment paradigms increasingly recognize that durable improvements in survival will depend upon integration of molecular diagnostics with biologically rational interventions rather than continued reliance upon conventional therapeutic intensification [10].

The translational biology of osteosarcoma further emphasizes that therapeutic resistance emerges through a remarkably interconnected network involving genomic instability, dysregulated signaling pathways, metabolic adaptation and immune evasion [11]. One of the most compelling observations emerging from contemporary genomic studies is the extraordinary complexity that characterizes osteosarcoma. Unlike many solid malignancies driven by recurrent actionable mutations, osteosarcoma exhibits extensive chromosomal rearrangements, structural variants and widespread genomic instability. Whole genome analyses have consistently demonstrated a predominance of catastrophic genomic events rather than singular oncogenic drivers, thereby creating remarkable intertumoral and intratumoral heterogeneity [12].

Genome wide association studies have identified susceptibility loci associated with osteosarcoma development, thereby providing compelling evidence that inherited constitutional factors contribute significantly to disease pathogenesis and may influence individual disease susceptibility [13]. Parallel advances in metastasis directed therapeutic development have demonstrated that pulmonary dissemination remains the predominant determinant of mortality and that successful therapeutic intervention must address biological processes governing tumour spread rather than primary tumour burden alone [14].

That being said,aberrant activation of intracellular signaling pathways contributes substantially to therapeutic resistance. Among these, dysregulation of the phosphatidylinositol 3 kinase and mammalian target of rapamycin signaling axis has emerged as one of the most consistently implicated mechanisms governing tumour proliferation, survival and chemotherapy resistance [15]. Nevertheless, the generally modest efficacy of pathway specific inhibitors suggests that signaling redundancy and compensatory molecular circuitry continue to limit clinical benefit.

Exome sequencing studies demonstrating mutational signatures reminiscent of homologous recombination deficiency suggest that subsets of osteosarcoma possess therapeutically exploitable DNA repair defects [16]. More recently, genome informed therapeutic approaches have proposed integration of comprehensive molecular profiling into individualized treatment paradigms and have identified several resistances associated pathways that may constitute actionable therapeutic vulnerabilities [17].

Now,distinct driver mutations involving histone genes have further reinforced the concept that epigenetic dysregulation contributes substantially to bone tumour biology and may provide additional mechanistic insights into osteogenic malignancies [18]. Likewise, demonstration of germline TP53 alterations among individuals with osteosarcoma has highlighted the critical contribution of impaired genomic surveillance and hereditary susceptibility to disease development and progression [19].

Earlier molecular investigations systematically catalogued recurrent cytogenetic abnormalities and targetable genomic alterations that collectively establish the genetic basis of tumour progression and therapeutic resistance [20]. Comprehensive evaluations of existing and emerging therapeutic strategies have simultaneously underscored the necessity of developing biologically informed interventions capable of overcoming intrinsic and acquired resistance mechanisms [21]. Epidemiological studies have additionally demonstrated that osteosarcoma predominantly affects children, adolescents and young adults, thereby emphasizing the profound clinical and societal consequences associated with therapeutic failure in this disease [22].

The metastatic phenotype of osteosarcoma is increasingly recognized as an adaptive evolutionary process governed by cellular selection and dynamic interactions with the tumour microenvironment. Molecular alterations associated with metastatic dissemination have identified several potentially targetable pathways and reinforced the notion that biological aggressiveness rather than local tumour burden principally determines clinical outcomes [23]. Elegant clonal tracing experiments have further demonstrated extensive intratumoral heterogeneity and evolutionary diversification during tumour progression, thereby providing mechanistic explanations for recurrence and treatment of refractoriness [24]. Complementing these findings, forward genetic screening approaches have identified previously unrecognized oncogenic drivers and metastatic pathways, substantially expanding the repertoire of candidate therapeutic targets [25,26].

Collectively, the evidence synthesized in this review supports an emerging conceptual model wherein osteosarcoma chemoresistance arises from the convergence of genomic instability, evolutionary diversification, stem cell plasticity, adaptive stress responses and intricate regulatory circuitry. These observations strongly advocate for a transition away from empiric therapeutic escalation toward precision oncology strategies founded upon comprehensive molecular characterization and individualized therapeutic intervention. Although substantial translational challenges remain, particularly with respect to tumour heterogeneity and pathway redundancy, the rapid expansion of genomic, transcriptomic and single cell technologies offers unprecedented opportunities to identify actionable vulnerabilities. Future therapeutic success in osteosarcoma will likely depend not upon further intensification of conventional cytotoxic therapy but upon the ability to decipher, anticipate and therapeutically circumvent the molecular architecture of resistance itself.

CONCLUSION

Osteosarcoma chemoresistance represents the cumulative consequence of genomic instability, clonal evolution, stem cell plasticity, adaptive stress responses and complex regulatory networks rather than a singular molecular aberration. The persistent stagnation in survival outcomes underscores the limitations of conventional therapeutic intensification and highlights the imperative for precision oncology based strategies. Future progress will depend upon integrating genomic, transcriptomic and single cell insights to identify actionable vulnerabilities and develop biologically informed interventions capable of circumventing resistance and improving long term clinical outcomes.

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