Review

Relationship between Osteosarcoma Therapy and Tumorigenesis, Metastasis, Immune Evasion, and Chemoresistance.

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Abstract: There has been no significant efficacy in treatment for osteosarcoma (OS) metastasis after nearly four decades of trials. This motivates us to elucidate OS therapies according to their four bidirectional mutation stages. To refresh the OS therapy status quo, the historical developments and clinical advancements are briefly described. However, the main issue of metastasis remains unresolved, accounting for 90% of pulmonary metastasis deaths. Thus, this metastasis problem is related to immune evasion and chemoresistance that are being induced after long-term treatment by the use of immunotherapy for tumorigenesis. Therefore, it is rationale to discuss the relationship cycles of mutation stages including tumorigenesis, metastasis, immune evasion, and chemoresistance. Even though many combinational and targeted therapies have been developed to intensify these mutation treatments, successful clinical translations with higher cure rates are still rare. Through this review, an in-depth understanding of the bidirectional relationship between the four OS mutation stages and their respective therapies is provided. Herein, we summarise the medicines used to treat tumorigenesis, including COLGALT2 inhibitors, Tra2B, and AGAP1, miR-148a and miR-21-5p EVs, and the lncRNA LIFR-AS1. Following the medicines used to treat metastasis are AXL, miR-135a-5p, mRNA BCL6, TGFβ1, Tim-3, SOCS5, CASC15, KLF3-AS1, PDCD4, ATG5, and Rab22a-NeoF1. Then the medicines used to treat immune evasion are N-cadherin, anti-IL-9, USP12 inhibitor, IgG-4$^+$ B-cells, LAP inhibitor, anti-Wnt2 mAb, anti-αvβ8 integrin, HK2-mediated IκBα, IDO inhibitor with NO, and TGF-βRII with anti-IgG1. Finally, the medicines used to treat chemoresistance are DHFR, FPGS, HSP-90AA1, XCT-790, ATKI, and IGF1. As a result, this contribution is expected to serve as a reference and guide for scientists and clinicians.

Keywords: Osteosarcoma; Tumorigenesis; Metastasis; Immune Evasion; Chemoresistance; Mutation.

1. Introduction

Osteosarcoma (OS) is a bone cancer that begins with a tumour secreted by the abnormal growth of the osteoid substances and immature bone [1]. OS primarily affects adolescents and elders in the age ranges of 15–19 [2] and over 65 [3], respectively. Although OS is a rare type of childhood cancer, it accounts for 3-5% of children's carcinomas and nearly 0.2% of all malignant tumours [4]. It has been revealed that a substantial (25%) portion of OS paediatric patients, while seeking medical help first, have metastases [5]. Around 15–20% of OS metastasis cases presented with the pulmonary tree and had an inferior clinical outcome [6]. Only about 20–30% of such metastatic cases live for a prolonged period, compared with 65–70% of localised cases [7].

Chemotherapy [8], immunotherapy [9], inhibitory therapy [10], and surgery [11] are the standard treatments for OS. Without proper treatments, OS diseases will progress to malignant tumours [12]. Over the course of five years, the overall and event-free survival

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rates are approximately 71% and 54%, respectively [13]. Due to the recurrence and metastasis incidences [14], the postmetastasis course over the five years for the overall and event-free survival rates are 38.1 ± 6.4% and 25 ± 5.3%, respectively [15]. Due to the fact that OS is the most common malignant bone tumour in adolescents, the 5-year survival rate drops to 70% and further decreases to 20–30% for patients with metastases [1]. Even after numerous trials done for nearly four decades, there has been no significant improvement in either localised or metastatic OS therapy [16]. In conclusion, the main cause of mortality is pulmonary metastases [15], which cause more than 90% of deaths [17].

Immunotherapy demonstrated high efficacy in clinical trials for tumorigenesis therapy [18], but after long-term treatments, it develops severe immunosuppressive and chemotherapeutic resistance in the tumour microenvironment (TME) [8]. This is due to OS's innate and acquired nature, which causes the therapy's progression to stall [19]. Scientists and clinicians have attempted to solve these problems for the past thirty years [20], but 30% of OS patients still do not respond to these standard treatments [21]. Therefore, combinational and targeted therapies [22][23] are developed for these problems and has a higher response rate [24]. However, their evidence of efficacy, long-term use [25], and personalised precision medicine [26] remain inadequate [27]. There is some evidence showing that immunosuppressive and chemotherapeutic resistance (chemoresistance) developed into immune evasion and multidrug resistance (MDR), respectively [28][29][30]. Despite these well-known immunotherapies, immune evasion, and chemoresistance, OS metastasis remains the primary barrier to achieving therapy efficacy [8]. Thus, more efficacious therapies and alternative therapeutic approaches are needed to intensify the treatments and achieve higher cure rates [31]. However, not much research has successfully provided an in-depth understanding of the relationship between tumorigenesis, metastasis, immune evasion, and chemoresistance.

Because the four stages are intertwined and complex [32], the focus of this review is on clarifying their relationship and encounter therapies. First of all, the status quo of OS therapies is presented, along with their historical development and clinical advancements. A comprehensive timeline is drawn to demonstrate significant discoveries and advancements in osteosarcoma studies. Besides, the summary of completed years for sarcoma clinical trials is tabulated to highlight the seminal discoveries and major clinical triumphs. In the content, the bidirectional relationship between these four OS mutation stages—tumorigenesis, metastasis, immune evasion, and chemoresistance—is clearly described. Further, short and precise definitions are given to each of them to reach a common understanding. Hereafter, their intertwined therapies could be discussed individually. Herein, it is notable that many clinically relevant therapies nowadays are combinational and multifunctional in order to cure the complex OS stages. Notably, intertwined therapy is a fact that should not be overlooked; however, it is prudent to discuss them by reconstructing them to elaborate precisely. Through this review, the stages and therapies of OS are precisely defined and clearly elucidated, which are expected to serve as guidance for scientists and clinicians.

2. Status Quo of Osteosarcoma Therapies

2.1. Historical Development

The significant discoveries and advancements in OS studies are drawn on a timeline as shown in Figure 1. The first in vivo test was done by Evans and Long (1922), who investigated the characteristic effects of the OS using the fresh anterior lobe [33]. After 42 years, the first gene cloned using human growth hormone (HGH) was done by Li and Liu (1964) [34]. After many trials, Jaffe et al. (1978) intended to use high-dose methotrexate to treat OS [35]. Rosen et al. (1982) pioneered preoperative adjuvant chemotherapy for OS to address the compliance issue associated with the previous high-dose therapy [36]. Furthermore, Zapf et al. (1984) investigated the biological and immunological properties of OS using insulin-like growth factors (IGF) [37]. The first in vitro test was done by

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Stashenko et al. (1987), who investigated a bone inhibitor using Interleukin (IL)-1β [38]. Bengtsson et al. (1993) were the first to use the recombinant technology for HGH [39]. Gentet et al. (1997) were the first to use the combined chemotherapy of etoposide and ifosfamide (EnI) that is commonly used in childhood OS now [40]. McGary et al. (2002) were the first to use the Tyrosine Kinase Inhibitor STI571 in targeted OS therapy [41]. Nardin et al. (2006) were the first to intend to target and activate macrophages by using liposomal muramyl tripeptide phosphatidylethanolamine in immunotherapy [42]. The OS stem cell studies using salinomycin inhibitor were pioneered by Tang et al. (2011) [43]. Finally, Gordon et al. (2019) were the first to successfully introduce an ABI-009 (nab-sirolimus) drug carrier for preliminary efficacy and safety results in the OS [44].

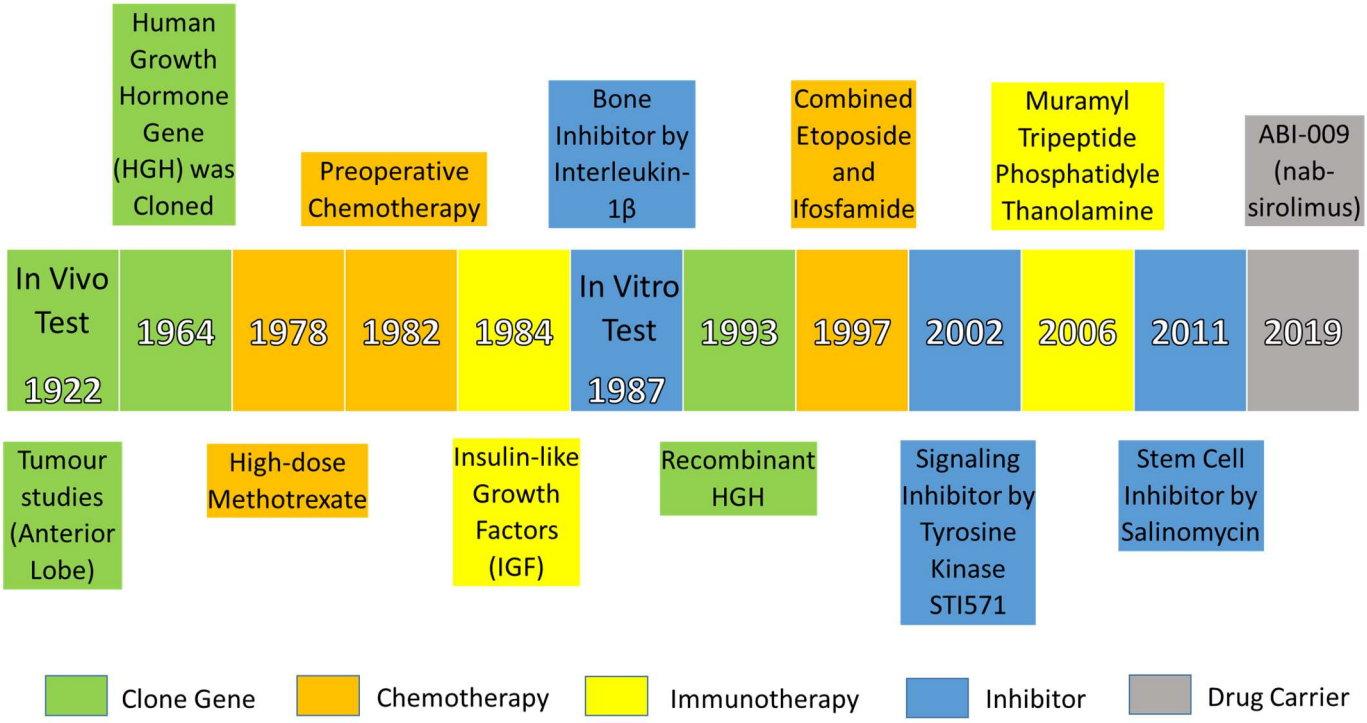

Figure 1. Timeline of significant discoveries and advancements in osteosarcoma studies.

2.2. Clinical Advancement

OS research is extremely hard and remains a global challenge. Despite the fact that many clinical trials had begun, the majority of them could not be completed. For the past twenty years, only ten clinical trials with federal government clinical trial identifiers (GCTI) have been successfully completed. Thus, the sarcoma types completed their clinical trials in years with API and primary tests as shown in Table 1. For all these trials, there are only two main types of OS: soft and solid, as observed in the table. The following active pharmaceutical ingredients (API) are appropriate for OS: topotecan (Tpt) [45], pazopanib (Pzp) [46], placebo (Plb) [47], gemcitabine (Gct) [48], M6620 [49][50], regorafenib (Rgf) [51][52], glembatumumab vedotin (GV) [53][54], lenvatinib [55], etoposide and ifosfamide (EnI) [56], nab-rapamycin (Rpm) [57][58], cyclophosphamide (Cfa) [59], simvastatin (Sim) [60], myeloid growth factor (MGF) [61], nab-paclitaxel [62][63], methotrexate (Mtx) [64], and doxorubicin (Dox) [65]. Besides, the primary tests, such as laboratory biomarker analyses [66] and dose escalation studies [67], were conducted for these successful triumphs. As a result, these two primary tests indicate the two main investigation parameters.

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Table 1. Summary of completed years for sarcoma clinical trials with their types, API, and primary tests.

No	Completed Year	GCTI	Sarcoma Type	API	Primary Test	Refs.
1	2022	NCT02357810	SSM	Tpt and Pzp	Laboratory Biomarker Analysis	[45][46]
2	2021	NCT01532687	Refractory Soft	Pzp, Plb, and Gct	Laboratory Biomarker Analysis	[47][48]
3	2022	NCT03718091	Advanced Solid	M6620 (VX-970)	Laboratory Biomarker Analysis	[49][50]
4	2022	NCT02048371	Selected Subtypes	Plb and Rgf	Laboratory Biomarker Analysis	[51][52]
5	2022	NCT02487979	RRS	GV in GPNMB carrier	Laboratory Biomarker Analysis	[53][54]
6	2022	NCT02432274	RRS Malignancies	Lenvatinib, EnI	Dose escalation study	[55][56]
7	2021	NCT03190174	Advanced	Nab-Rpm in Nvl carrier	Dose escalation study	[57][58]
8	2020	NCT02390843	RRS	Cfa, Sim, Tpt, and MGF	Dose escalation study	[59][60]
9	2019	NCT01962103	RRS	Nab-paclitaxel	Dose escalation study	[62][63]
10	2005	NCT00180908	Solid	EnI, Mtx, and Dox	Laboratory Biomarker Analysis	[64][65]

Abbreviations: SSM, soft and solid metastatic; RRS, refractory and relapsed solid; Pzp, pazopanib; Tpt, topotecan; Gct, gemcitabine; Plb, placebo; Rgf, regorafenib; GV, glembatumumab vedotin; GPNMB, Glycoprotein non-metastatic melanoma protein B; EnI, etoposide and ifosfamide; Rpm, Rapamycin; Nvl, Nivolumab; Sim, simvastatin; Cfa, cyclophosphamide; MGF, myeloid growth factor; Mtx, methotrexate; Dox, doxorubicin

3. Osteosarcoma Bidirectional Mutation Stages

OS therapies are difficult because they progress and reverse through four mutation stages and are intertwined, including tumour microenvironment (TME), metastasis, immune evasion, and chemotherapeutic resistance, as shown in Figure 2. The bidirectional complexity of progression and reversion in OS mutation stages is influenced by the exosomes of tumour, stem, mesenchymal, immune, fibroblast, and endothelial cells [68]. There is mounting evidence that signal molecules such as neurotransmitters, enzymes, hormones, and nucleic acids [69] are involved in the angiogenesis, growth, migration, metastasis, and apoptosis of the above mentioned cells, involving intercellular cell communication, body regulation, and immune responses [70]. In this cellular communication, extracellular vesicles (EV) play a key role [71], which could be derived by various cells such as OS cells, mesenchymal stem cells (MSC), adipose-derived MSC (ADMSC), cancer-associated stromal fibroblasts (CAF), and macrophages [72]. These EV regulate the activity of recipient cells, including angiogenesis, proliferation, invasion, migration, metastasis, chemotherapeutic resistance, and apoptosis, by using their cargoes of proteins, DNA, and RNA [73]. These three cargoes have distinct metabolic dynamics [74] including a connection with the EV components' biogenesis machinery, a cellular homeostasis regulator with cytoplasmic DNA sensor activation, and parental cell function efficiency at different states [75]. The creation of biomarker vehicles [76] that employ the aforementioned pro-tumorigenic components and signalling pathways to circulate immune responses from OS cancer diseases remains a significant clinical trial challenge [77].

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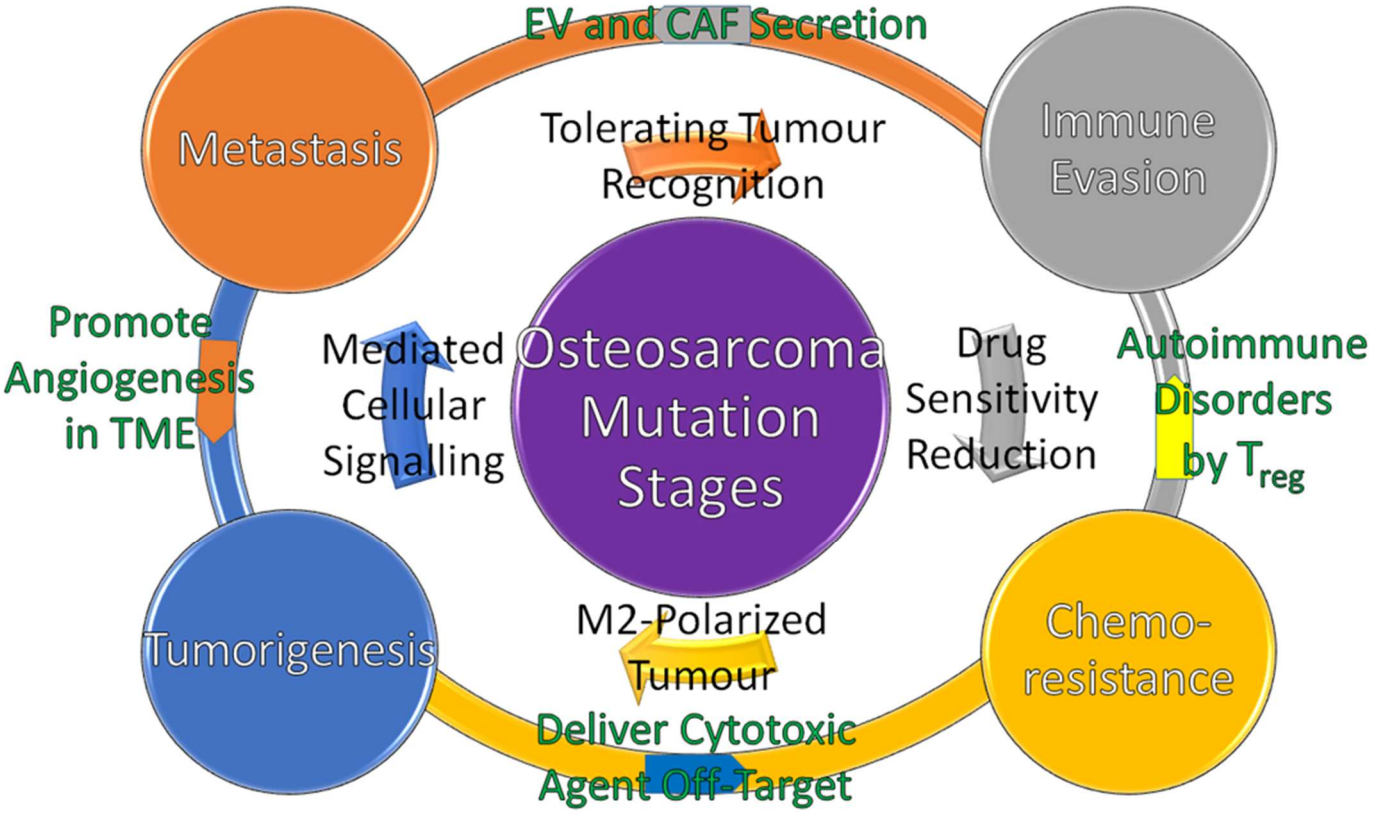

Figure 2. Schematic of bidirectional osteosarcoma mutation stages.

3.1. Tumorigenesis

TME is composed of EV secretion cells, MSC, and tumour cells. The EV cells are secreted by MSC and immune cells to alter macrophage phenotype-2 (M2) [78] and regulate tumour progression via the Wnt signalling pathway [79]. Furthermore, the EV cells are the paracrine factors secreted by human bone marrow MSC (BMSC), such as osteoclasts, osteoblasts, and endothelial cells, to regulate tumour cells via communication with the Hedgehog signalling pathway [80]. As a result, the M2 and tumour cells regulate TME by EV secretions in order to promote angiogenesis, growth, and metastasis [81][82]. Basically, the tumorigenesis research in TME is concerned with how coexisting cells interact and communicate with one another.

3.2. Metastasis

The metastasis potential is affected by the communication between the stressed MSC and the micro RNA (miRNA) content of EV. Tumour cells metastasize in three ways: by secreting EV, by influencing TME, and by mediating the transformation of distant MSC. Direct EV secretion by osteoblasts and CAF can improve migrability. The induction of metastasis can be influenced by regulating tumour and MSC oncogenic phenotypes in TME. The pro-angiogenic factors from endothelial cells can mediate EV transformation to modulate cell invasiveness and promote metastasis. Metastasis could be activated either by modulating tumour-associated macrophage (TAM) cellular signalling to promote the M2 or by producing transforming growth factor beta (TGFβ)-2 to create an immunosuppressive and pro-TME [83]. As a result, the tumour cells could be metastasized by inducing a pro-metastatic and tumorigenic phenotype and mediating transformation into local or distant cells.

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3.3. Immune Evasion

The immune system is divided into innate and adaptive immunizations, which are always related to the bone microenvironment [84]. The immune evasion occurred because the inefficient immune cells allowed the tumours to evade the immune surveillance systems or the host immune checkpoint through multiple mechanisms [24]. This inefficiency induced a tolerance for the T-cell receptor (TCR), resulting in a dormant response to tumour recognition [85]. Therefore, the tumour cancer cells in TME escaped immunotherapy. However, this peripheral tolerance of host-cell immune responses is protected by regulating T regulatory cells (T_{reg}) to prevent autoimmune disorders [86]. In fact, two major mechanisms induce immune tolerance [87]: T-cell-mediated inflammation suppression and no tumour signals received by the major histocompatibility complex (MHC) antigen presentation [88]. Traditionally, the plasma protease thrombin cleaves glycoprotein A repetitions predominant (GARP) in tumour immune evasion to release active TGFβ [89]. TGFβ is the main coordinator and mediator between both mechanisms mentioned in immune evasion [90]. TGFβ increased programmed cell death protein (PD) ligand-1 expression on TAM [91] to bind with PD-1 (CD279) for cytotoxic T lymphocyte-associated antigen (CTLA)-4 inhibition. CTLA4 (CD152) is a membrane glycoprotein of immunosuppressive T_{reg} that binds to costimulatory molecules CD80 and CD86 to inhibit early T cell (CD8+ and CD4+) activation [92]. These T cells are anti-tumour cells that respond to cancer-associated fibroblasts (CAFs) for immune evasion regulation [93].

3.4. Chemoresistance

Chemoresistance is chemotherapeutic resistance, resulting in a chemotherapeutic efficacy deficit [94]. It always results in cytotoxic agents being minimally delivered or severely off-target, destroying therapeutic compliance effects [95]. Chemoresistance in cancer cells can be either inherent or acquired, with the latter increasing proportionally with the duration of the therapy [96]. Chemoresistance is commonly known as MDR, which is drug resistance to Mtx, Dox, and CDDP drugs [97]. Drug accumulation in clone and stem cells altered TME, leading to mutation and decreased drug sensitivity [98]. For instance, chemoresistance decreased Dox sensitivity, resulting in M2 induction, which caused tumour cells to spread without responsiveness to Dox [99]. However, the sensitivity of drugs can be induced by the transfer of specific bioactive molecules, such as non-coding RNA and proteomic signatures [100].

4. Recent Osteosarcoma Therapies

Because there have been numerous OS therapies over the last four decades, only the five most recent years are considered below. Despite the fact that many OS therapies have been developed, their individual and combinational mechanisms are dispersed [101]. Therefore, a schematic is drawn to elucidate their recent medicines and therapy mechanisms in OS, as shown in Figure 3. Medicines used to inhibit and suppress tumorigenesis, metastasis, immune evasion, and chemoresistance via communication mediums [102]. Targeted therapies can be developed to intensify the therapies and achieve higher cure rates by having a thorough understanding of the roles of genes in communication axes and signalling pathways [103].

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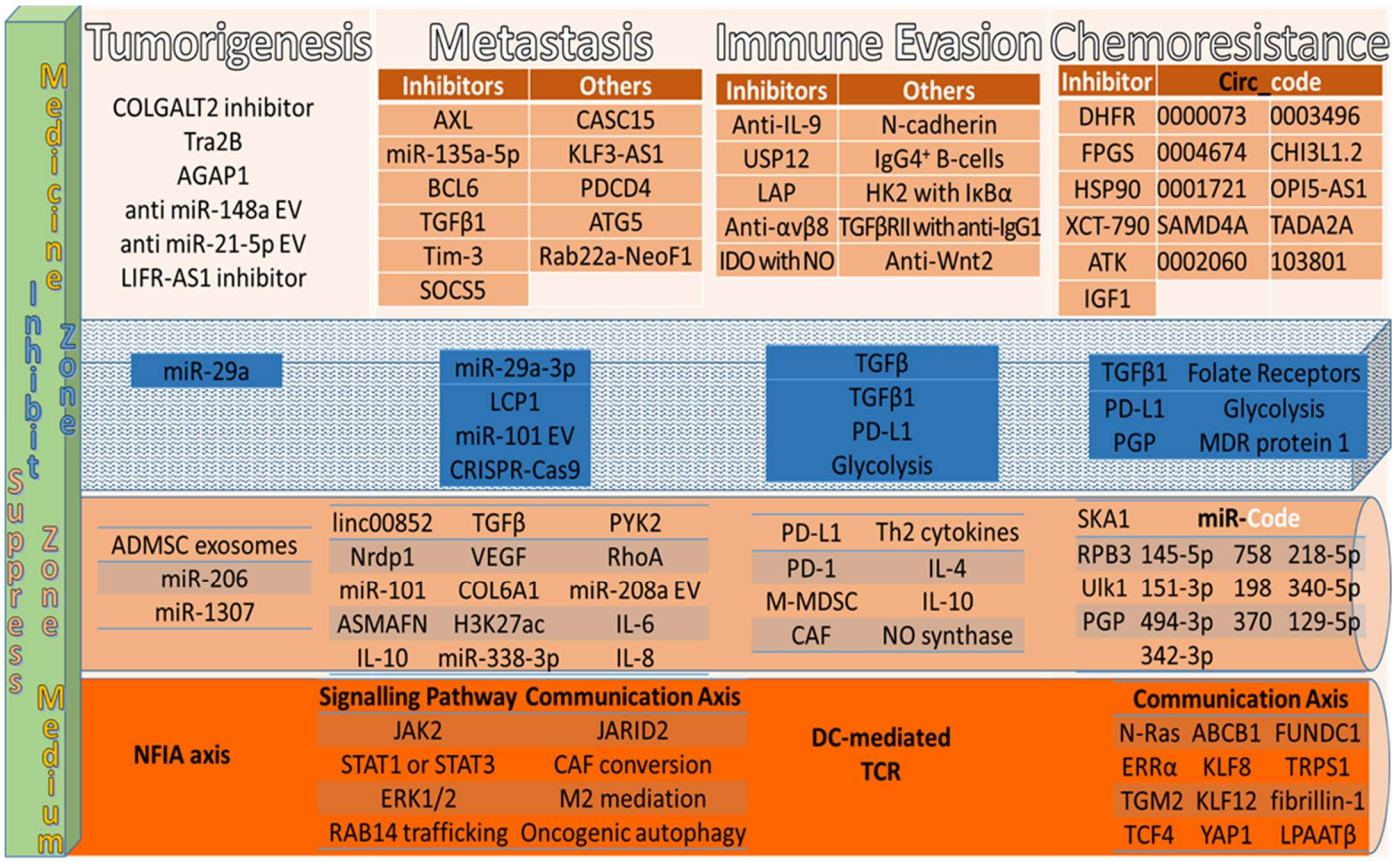

Figure 3. Schematic of recent osteosarcoma medicines and their therapy mechanisms for tumorigenesis, metastasis, immune evasion, and chemoresistance.

4.1. Tumorigenesis Therapies

The tumorigenesis therapies are generally medicated in connection with the suppressive, regulative, and inhibitive treatment mechanisms [104]. There is a summary of ten recent studies that have addressed tumorigenesis with medicines for their treatment mechanisms, as shown in Table 2. For instance, six studies used suppressive mechanism treatments to halt tumorigenesis' proliferation, migration, and invasion. Collagen beta (1-O) galactosyl transferase 2 (COLGALT2) inhibitor [105][106], transformer 2β (Tra2B) [107][108], and ArfGAP with GTPase domain 1 (AGAP1) [109][110] were used as the medicines to suppress ADMSC exosomes, miR-206, and miR-1307, respectively. In studies of chondrogenesis like osteoclast differentiation and bone resorption activity, the miR-148a and miR-21-5p EVs were used increase their genes to mimic umbilical vein endothelial cell (UVEC) formation in TME [81][111]. Furthermore, long non-coding RNA (lncRNA) leukaemia inhibitory factor receptor antisense RNA1 (LIFR-AS1) inhibitor was used to inhibit miR-29a in the the nuclear factor IA (NFIA) axis to suppress human peripheral-blood monocytes (THP-1)-induced macrophage-derived exosomes (MDE) [112][113]. All ten studies are related to the exosomal-derived genes and these could be used as diagnosis and prognosis markers in OS progression [114].

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Table 2. Summary of medicines for tumorigenesis with treatment mechanisms.

Medicine	Tumorigenesis	Treatment Mechanisms	Ref.
COLGALT2 inhibitor	Proliferation, migration, and invasion	Suppress ADMSC exosome-mediated	[105][106]
Tra2B		Suppress BMSC-derived exosomal miR-206	[107][108]
AGAP1		Suppress OS cell-derived exosomal miR-1307	[109][110]
miR-148a and miR-21-5p EVs	Chondrogenesis	Increase genes to mimic UVEC formation in TME	[81][111]
LIFR-AS1 inhibitor	Progression	Inhibit miR-29a in the NFIA axis	[112][113]

4.2. Interfere Communication Mediators' Therapies

Metastasis is stimulated and controlled by intercellular communication in endothelial cells [115]. By interfering with their direct and indirect communication mediators against endothelial changes, both stages can be inhibited [116]. There is a summary of twenty recent studies that have addressed metastasis with medicines that interfere with communication mediators in signalling pathways, as shown in Table 3. For instance, twelve studies interfered with communication mediators using inhibitors, including AXL receptor tyrosine kinase (AXL) [117][118], miR-135a-5p [119][120], messenger RNA (mRNA) B-cell lymphoma-6 (BCL6) [121][122], TGFβ1 [123][124], T-cell immunoglobulin and mucin-domain containing protein-3 (Tim-3) [125][126], and suppressor of cytokine signalling-5 (SOCS5) [127][128]. These inhibitors interfered with miR-29a-3p, BMSC-derived exosomal lymphocyte cytosolic protein-1 (LCP1), miR-101 EV, CRISPR-associated protein-9 (Cas9), M2 mediation, and signal transducers and activators of transcription (STAT)-1 mediation by suppressing long intergenic non-protein coding RNA (linc)-00852 in the jumonji and AT-rich interaction domain containing 2 (JARID2) axis; neuregulin receptor degradation protein-1 (NRDP1) in the Janus kinase-2 (JAK2)/STAT3 signalling pathway; ADMSC-derived miR-101; CAF and α-smooth muscle actin expression and fibronectin (ASMAFN) differentiation; IL-10, TGFβ, and vascular endothelial growth factor (VEGF) secretions; and collagen type VI alpha 1 (COL6A1) from histone3 lysine27 acetylation (H3K27ac) activated in CAF conversion with IL-6 and IL-8 secretions; respectively.

The other eight studies interfered with communication mediators using other medicines, such as cancer susceptibility 15 (CASC15) or KLF3 antisense RNA 1 (KLF3-AS1) [129][130], programmed cell death 4 (PDCD4) [131][132], autophagy-related gene 5 (ATG5) [133][134], and Rab22a-NeoF1 fusion protein [135][136]. Other medicines interfered with Ras-associated binding 14 (RAB14), extracellular signal-regulated kinase-1/2 (ERK1/2) signalling pathway, oncogenic autophagy, and M2 with Arginylglycylaspartic acid (RGD) peptide internalisation in STAT3 by suppressing miR-338-3p; miR-208a EV; BMSC-derived EV; and protein tyrosine kinase-2 (PYK2) and Ras homolog family member A (RhoA); respectively. All of the medicines used in the 20 studies interfered with communication mediators related to EV secretions or protein expression.

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Table 3. Summary of medicines that interfere communication mediators' therapies.

Medicine	Interfere Communication Mediator in Signalling Pathway	Ref.
AXL inhibitor	Interfere miR-29a-3p by suppressing linc00852 in JARID2 axis	[117][118]
miR-135a-5p inhibitor	Interfere BMSC-derived exosomal LCP1 by suppressing Nrdp1 in JAK2/STAT3 signalling pathway	[119][120]
BCL6 inhibitor	Interfere miR-101 EV by suppressing ADMSC-derived miR-101	[121][122]
TGFβ1 inhibitor	Interfere CRISPR-Cas9 by suppressing CAF and ASMAFN differentiation	[123][124]
Tim-3 inhibitor	Interfere the M2 mediation by suppressing IL-10, TGFβ, and VEGF secretions	[125][126]
SOCS5 inhibitor	Interfere STAT1 mediation by suppressing COL6A1 from H3K27ac activated in CAF conversion with IL-6 and IL-8 secretions	[127][128]
CASC15 or KLF3-AS1	Interfere RAB14 trafficking by suppressing miR-338-3p	[129][130]
PDCD4	Interfere ERK1/2 signalling pathway by suppressing miR-208a EV	[131][132]
ATG5	Interfere oncogenic autophagy by suppressing BMSC-derived EV	[133][134]
Rab22a-NeoF1	Interfere M2 with RGD peptide internalisation in STAT3 by suppressing PYK2 and RhoA	[135][136]

4.3. Immune Evasion Therapies

The suppression and communication barriers of immune cells allow immune evasion [137]. Tumour cells escape being destroyed by the immune system because the immune cells, such as neutrophils, monocytes, macrophages, dendritic cells, natural killer cells, and B and T lymphocytes, are suppressed [138]. Besides, the tumour immune responses are barred from immune checkpoint activations, thereby causing immune evasion [139]. Therefore, the immune evasion is eliminated by suppressing and inhibiting the both mechanisms. There is a summary of twenty recent studies with medicines and prevention mechanisms for immune evasion, as shown in Table 4. For instance, twelve studies used medicines to suppress immune evasion mechanisms, such as mRNA N-cadherin [140][141], anti-IL-9 [142][143], ubiquitin-specific peptidase 12 (USP12) inhibitor [144][145], immunoglobulin G1 monoclonal antibody (IgG)-4^{+} B-cells [146][147], latency-associated peptide domain (LAP) inhibitor [148][149], and anti-Wnt2 mAb [93][150]. These medicines suppressed PD-L1, PD-1, IL-4, IL-10, monocytic myeloid-derived suppressor cells (M-MDSC), NO synthase, and CAF in order to activate CD8^{+} T cells and TCR. The remaining eight studies used medicines to inhibit immune evasion mechanisms, such as anti-$\alpha v\beta 8$ integrin (also known as ADWA-11) [151][152], hexokinase-2 (HK2)-mediated phosphorylation of i-kappa-b-alpha (IκBα) [153][154], indoleamine 2,3-dioxygenase (IDO) inhibitor with NO [155][156], and TGFβ receptor II (TGFβRII) with anti-IgG1 (also known as bintrafusp alfa) [157][158]. These medicines inhibited the expression of TGFβ, TGFβ1, PD-L1, and glycolysis in order to activate CD8^{+} T cells and T_{reg} cells. In all 20 studies, ignoring the immune evasion due to innate and adaptive immunizations, the medical therapies are focused on the activation of immune cells, such as CD8^{+} T cells, TCR, and T_{reg} cells. As a result, immune evasion is prevented by checkpoint blockade therapy [159], such as PD-L1, PD-1, IL-4, IL-10, M-MDSC, NO synthase, CAF, TGFβ, and TGFβ1 [160].

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Table 4. Summary of immune evasion medicines with their prevention mechanisms.

Medicine	Prevention Mechanisms	Ref.
mRNA N-cadherin	Suppress PD-L1 to reduce immunosuppression and tumorigenesis	[140][141]
Anti-IL-9	Suppress IL-10 expression and tumour infiltrating T cells	[142][143]
USP12 inhibitor	Suppress M-MDSC, NO synthase, and PD-L1 to activate $CD8^+$ T cells to stabilise p65	[144][145]
$IgG4^+$ B-cells	Suppress Th2 cytokines IL-4 and IL-10	[146][147]
LAP inhibitor	Suppress PD-1 to activate $CD8^+$ T cells with effector molecule phenotypes	[148][149]
Anti-Wnt2 mAb	Suppress CAF and PD-1 to activate DC-mediated anti-tumour TCR	[93][150]
Anti-$\alpha v\beta 8$ integrin	Inhibit TGFβ or TGFβ1 immunosuppression to activate TCR or T_{reg} cells	[151][152]
HK2 with IκBα	Inhibit PD-L1 expression and activate $CD8^+$ T-cell	[153][154]
IDO inhibitor with NO	Inhibit glycolysis to increase the functions of $CD8^+$ T-cells and T_{reg} cells	[155][156]
TGFβRII with anti-IgG1	Inhibit TGFβ and PD-L1	[157][158]

4.4. Chemoresistance Therapies

Chemoresistance therapies are always accompanied by treatments for severe off-target effects to restore therapeutic compliance [161]. The acquired nature of chemoresistance in cancer cells will minimise the cytotoxic agent's delivery proportionally to the chemotherapeutic treatment duration [162]. Hence, this becomes a primary challenge for therapeutic agents and cellular lesions in osteosarcoma therapy [8]. Drug accumulation in cells, intracellular detoxification, apoptosis, DNA repair, signal transduction disruption, and tumour stem cell immunity all contribute to chemoresistance [163]. The majority of therapeutic approaches involve inhibition of the oncogene's expression to interfere with or mute the communication pathways or axis [164]. Some use drug carriers to avoid rapid drug clearance and prolong release [165][166]. As a result, chemoresistance therapies should focus on oncogene inhibition, drug influx and efflux, and drug carriers [167].

Chemoresistance therapies are divided into two types: inhibitor therapies and gene knockdown therapies. There is a summary of ten recent studies that used inhibitor therapies for different types of drug resistance and their chemoresistance prevention in osteosarcoma cells, as shown in Table 5. For instance, there are four studies focused on reducing folate receptors for Mtx and Dox drug resistance. Dihydrofolate reductase (DHFR) [168][169] and folylpoly-γ-glutamate synthetase (FPGS) [170][171] inhibitors were used to induce cancer cell apoptosis and inhibit the interaction of spindle and kinetochore associated complex subunit 1 (SKA1) and RNA polymerase II subunit 3 (RPB3), respectively. DHFR reduced the affinity of methotrexate resistance by converting dihydrofolate to tetrahydrofolate in order to inhibit purine and thymidine synthesis, resulting in a deficit in DNA replication and apoptosis. Another two studies of cis-diamminedichloroplatinum (II) (CDDP or cisplatin) drug resistance used the heat shock protein (HSP)-90AA1 gene inhibitor [172][80] to deactivate autophagy activating kinase 1 (Ulk1) in FUN14 domain-containing protein 1 (FUNDC1) mediation for mitophagy activation to induce apoptosis. Mitophagy is mitochondrial removal through autophagy, which allows tumour cells to survive cellular stress by clearing damaged organelles and proteins. Two studies of P-glycoprotein (PGP) were inhibited by the inverse agonist XCT-790 or the anlotinib tyrosine kinase (ATK) inhibitor [173][174] for mRNA ATP-binding cassette subfamily B member 1 (ABCB1) in the oestrogen-related receptor alpha (ERRα) axis. Another two studies of ABCB1 in the ERRα axis were inhibited by insulin-like growth factor 1 (IGF1) [175][176] in order to reverse metabolic disorders. As a result, folate receptors, FUNDC1-mediated Ulk1, and ABCB1 in the ERRα axis are the key targets in chemoresistance therapies.

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Table 5. Summary of inhibitors, drug resistance, and their chemoresistance prevention in osteosarcoma cells.

Inhibitor	Resistance	Chemoresistance Prevention	Ref.
DHFR	Mtx and Dox	Reduce folate receptors to induce apoptosis in cancer cells	[168][169]
FPGS	Mtx	Reduce folate receptors by inhibiting the interaction of SKA1 and RPB3	[170][171]
HSP90	CDDP	Inhibit Ulk1 in FUNDC1 mediation for mitophagy activation	[172][80]
XCT-790 or ATK	Dox	Inhibit PGP for ABCB1 in the ERRα axis	[173][174]
IGF1	Dox	Inhibit ABCB1 in the ERRα axis to reverse metabolic disorder	[175][176]

Despite the above key targets in chemoresistance therapies, the expression of siRNA oncogenes has been popularly used recently to interfere with or mute the communication pathways or axis [177]. There is a summary of twenty recent studies that used siRNA gene knockdown therapies for different types of drug resistance and their chemoresistance prevention in osteosarcoma cells, as shown in Table 6. Transmitting circular RNA (circ_) is used to prevent the Mtx, Dox, and CDDP drug resistance in the four, ten, and six studies, respectively. For Mtx instances, the circ_0000073 [178][179] and circ_0081001 [180][181] gene knockdowns inhibited the N-Ras pathway by sponging miR-145-5p and miR-151-3p and the transglutaminase-2 (TGM2) axis by miR-494-3p, respectively. For Dox instances, the gene knockdowns of circ_0004674 [182][183], circ_0001721 [184][185], circ_SAMD4A (sterile alpha motif domain) [186][187], circ_0002060 [188][189], and circ_0003496 [190][191] inhibited the fibrillin-1 axis by sponging miR-342-3p, the transcription factor 4 (TCF4) axis by miR-758, the Krüppel-like factor (KLF)-8 axis by miR-218-5p, the ABCB1 axis by miR-198, and the KLF12 axis by miR-370, respectively. For CDDP instances, the gene knockdowns of circ_CHI3L1.2 (chitinase 3-like 1.2) or lncRNA OPI5-AS [192][193], circ_TADA2A (transcriptional adaptor 2A) [194][195], and circ_103801 [196][197] inhibited the lysophosphatidic acid acyltransferase β (LPAATβ) axis by sponging miR-340-5p, the yes-associated protein (YAP) and trichorhinophalangeal syndrome 1 (TRPS1) axis by miR-129-5p, and the MDR-associated protein 1 and PGP, respectively. As a result, the communication pathways of chemoresistance in osteosarcoma cells would be more effectively prevented by the therapies targeting oncogene expression with their knockdowns.

Table 6. Summary of gene knockdowns, drug resistance, and their chemoresistance prevention in osteosarcoma cells.

Gene Knockdown	Resistance	Chemoresistance Prevention	Ref.
circ_0000073	Mtx	Inhibit N-Ras pathway by sponging miR-145-5p and miR-151-3p	[178][179]
circ_0081001	Mtx	Inhibit TGM2 axis by sponging miR-494-3p	[180][181]
circ_0004674	Dox	Inhibit fibrillin-1 axis by sponging miR-342-3p	[182][183]
circ_0001721	Dox	Inhibit TCF4 axis by sponging miR-758	[184][185]
circ_SAMD4A	Dox	Inhibit KLF8 axis by sponging miR-218-5p	[186][187]
circ_0002060	Dox	Inhibit ABCB1 axis by sponging miR-198	[188][189]
circ_0003496	Dox	Inhibit KLF12 axis by sponging miR-370	[190][191]
circ_CHI3L1.2 or OPI5-AS1	CDDP	Inhibit LPAATβ axis by sponging miR-340-5p	[192][193]
circ_TADA2A	CDDP	Inhibit TRPS1 and YAP1 axis by sponging miR-129-5p	[194][195]
circ_103801	CDDP	Inhibit MDR-associated protein 1 and PGP	[196][197]

5. Conclusions

Despite the innate and acquired nature of OS, its progression is intertwined, including cycles of tumorigenesis, metastasis, immune evasion, and chemoresistance. Firstly,

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tumorigenesis is the result of M2 alterations, which are progressed via signalling pathways by the MSC- and immune cell-secreted EV. Secondly, metastasis is potently affected by the communication between the stressed MSC and the miRNA content of EV. Thirdly, immune evasion occurred because tumour cells evaded the host immune checkpoint through the TCR tolerance mechanism, resulting in T_{reg} in autoimmune disorders. Finally, chemoresistance causes cytotoxic agents to be delivered severely off-target, resulting in a chemotherapeutic efficacy deficit. These four stages of progression are treated by the combinational and multifunctional therapies listed below. Ten tumorigenesis therapy studies have been conducted using medicines such as COLGALT2 inhibitors, Tra2B, and AGAP1, miR-148a and miR-21-5p EVs, and the lncRNA LIFR-AS1 inhibitor. The mechanisms of tumorigenesis were being suppressed, regulated, and inhibited, such as proliferation, migration, invasion, chondrogenesis, and UVEC formation. Their targets include ADMSC exosomes, miR-206, miR-1307, miR-148a, miR-21-5p, and miR-29a in the NFIA axis. Metastasis therapies are treated with medicines related to EV secretions and protein expression for intercellular communication in endothelial cells. There have been twenty therapy studies using inhibitor and disruptor medicines to inhibit pro-tumorigenic expression and disrupt signalling pathways. AXL, miR-135a-5p, mRNA BCL6, TGFβ1, Tim-3, and SOCS5 are the inhibitor medicines. These medicines inhibit miR-29a-3p and linc-00852 in the JARID2 axis, LCP1 and NRDP1 in the JAK2/STAT3 signalling pathway, miR-101 EV, Cas9 in CAF and ASMAFN differentiation, IL-10, TGFβ, and VEGF secretions for M2, and CAF conversion with COL6A1 and H3K27ac in the STAT1 signalling pathway. CASC15, KLF3-AS1, PDCD4, ATG5, and Rab22a-NeoF1 are the disruptor medicines. These medicines disrupt RAB14 by miR-338-3p, the ERK1/2 signalling pathway by miR-208a EV, oncogenic autophagy by BMSC-derived EV, and M2 with RGD in STAT3 by PYK2 and RhoA. Immune evasion is treated by activating $CD8^+$ T cells and connecting TCR and T_{reg} cells for immune checkpoint activations and communication checkpoint regulations, respectively. Twenty therapy studies have been conducted using medicines to suppress and inhibit immune evasion mechanisms. These medicines are mRNA N-cadherin, anti-IL-9, USP12 inhibitor, IgG-4^+ B-cells, LAP inhibitor, anti-Wnt2 mAb, anti-αvβ8 integrin, HK2-mediated IκBα, IDO inhibitor with NO, and TGFβRII with anti-IgG1. Medical targets include PD-L1, PD-1, IL-4, IL-10, M-MDSC, NO synthase, CAF, TGFβ, and TGFβ1. Chemoresistance therapies use oncogene inhibition as well as drug carriers for influx and efflux to repair immune therapies and disrupt communication pathways. There are thirty studies of chemoresistance therapies focused on Mtx, Dox, and CDDP drug resistance by using inhibitor therapies and gene knockdown therapies. The inhibitors are DHFR, FPGS, HSP-90AA1, XCT-790, ATKI, and IGF1. The inhibitor's targets are folate receptors, FUNDC1-mediated Ulk1, and ABCB1 in the ERRα axis. Besides, the gene knockdowns are circ_0000073, circ_0081001, circ_0004674, circ_0001721, circ_SAMD4A, circ_0002060, circ_0003496, circ_CHI3L1.2 or lncRNA OPI5-AS, circ_TADA2A, and circ_103801. The gene knockdown's targets are miR-145-5p and miR-151-3p in the N-Ras pathway, miR-494-3p in the TGM2 axis, miR-342-3p in the fibrillin-1 axis, miR-758 in the TCF4 axis, miR-218-5p in the KLF-8 axis, miR-198 in the ABCB1 axis, miR-370 in the KLF12 axis, miR-340-5p in the LPAATβ axis, miR-129-5p in the YAP/TRPS1 axis, and the MDR-associated protein 1 and PGP. In conclusion, all these OS therapies are individually elucidated to treat tumorigenesis, metastasis, immune evasion, and chemoresistance, but their OS mutation stages are bidirectional and intertwined, resulting in their being combinational and multifunctional.

6. Challenges and Future

OS is an unusual and complicated malignant tumour that necessitates an integrative and interdisciplinary therapeutic approach [198]. It has been reported that a multidisciplinary approach requires collaboration and cooperation between paediatric or medical cancer specialists, surgeons, pathologists, radiologists, and radiotherapists [5]. Thus, several models of OS neoplasm have diverse clinical outcomes [199], making the diagnosis

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and treatment of OS cancer extremely challenging. Thereby, the therapeutic regimen for OS patients has not been systematized, harmonized, or standardized [200]. It has been reported that thorough surgical eradication of all sites of primary and metastatic OS is obligatory, foretelling better clinical end-results and continuity of quality life [5]. However, those OS cases have several primary and metastatic OS disease locations that are not manageable for total surgical resection and result in impecunious clinical consequences. Furthermore, preoperative chemotherapies cause chemoresistance, resulting in a two-fold increase in the cisplatin capability of mutational load in OS cases [201]. As a result, chemotherapeutic regimens for recurring or replacement cases of chemotherapy resistance are constantly being improved [202].

According to a recent study, the genetic framework and oncogenesis process of OS are largely unknown, which is impeding research efforts. The immune microenvironment of OS tumours has been extensively studied. It found that OS possesses noticeable diversity and a complicated all-around mode of process regarding malignancy continuation and metastasis [138]. Another study reported that MDSCs massively invade OS tumours and promote anti-cancer immune-suppressive activities [138][203][204]. Research studies said that preoperative chemotherapy agents, e.g., dox, CDDP, and ifosfamide, effectively brought down the MDSC count in OS cases and, after that, augmented both immune sensitivities and the overall immune system [205]. Metformin has been shown in studies to effectively reduce OS tumour progression and size. Metformin also shows substantial activity in reducing polymorphnuclear MDSC; nevertheless, no considerable variability was observed for M-MDSC [206]. Sodium-glucose cotransporter 2 (SGLT2) is a principal intercessor of epithelial glucose transport. It has been proclaimed that SGLT2 is vigorously and exaggeratedly exhibited in several malignant tumour cells, including OS [207]. Antagonizing overexpressed SGLT2 appreciably hinders cancer advancement, e.g., breast cancer, cervical cancer, hepatocellular cancer, prostate cancer, and lung cancer [208]. Although the anti-malignant pharmacodynamics of SGLT2 antagonists in OS malignancy remain imprecise [207][208][209]. This narrative review advocates more research regarding this malignancy and safeguards our children and adults from the atrocities of this cancer.

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