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Review article

The use of heparin and heparin-like molecules in cancer treatment: a review

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ABSTRACT

Background: Heparin and heparin-like molecules have shown some promise in the treatment of several cancers. These molecules have roles in angiogenesis, cell proliferation, immune system modulation, cell migration, and cellular invasion. The pathways and mechanisms used by these molecules to inhibit the proliferation of cancer cells aid in understanding the utilization of these molecules in potential treatments. Our aim is to review the use of heparin and heparin-like molecules in cancer treatment, explore the results, and discuss their potential downfalls.

Methods: Publications on heparin and heparin-like molecules and compounds were collected from the PubMed and EMBASE databases. Boolean operators and MeSH terms related to heparin, heparin-like molecules, and cancer were used to conduct this search. The articles were reviewed by the authors.

Results: Several heparin mimetics are showing promise in cancer treatment. Various studies using mimetics alone or in combination with chemotherapy have been conducted and have yielded mixed results. They work on multiple target molecules, mostly receptors such as fibroblast growth factor and endothelial growth factor. The main types of cancers targeted by these drugs are multiple myeloma, pancreatic cancer, hepatocellular carcinoma (HCC), and other solid tumors.

Conclusion: Although limited clinical evidence of efficacy and potential pitfalls are present, heparin and heparin-like molecules have shown potential in the management of cancer patients. Additional research is required to fully understand the biological mechanisms utilized by these molecules in cancer treatment.

List of Abbreviations

Unfractionated heparin: UFH
Low molecular weight heparin: LMWH
Heparin sulfate proteoglycans: HSPGs
Glucosamine: GlcN
Glucuronic acid: GlcA
Iduronic acid: IdoA
Mitogen-activated protein kinase: MAPK
Fibroblast growth factors: FGFs
Human Growth Factor: HGF
Vascular Endothelial Growth Factor: VEGF
Endothelial Growth Factor Receptor: EGFR
Sonic Hedgehog: SHH

Introduction

Heparin and heparin-like molecules form a group of proteins that are involved in many pathways and play an important role in diverse biological processes such as proliferation, development, inflammation, and disease [1]. Heparin and heparin-like molecules bind to a vast array of proteins because of their structural variety and conformational flexibility that these structures possess [2], revealing a strong structure-function relationship. The use of heparin and low-molecular-weight heparin (LMWH) in cancer treatment began recently and both have shown some promise in their ability to attenuate the damage caused by various cancers such as pancreatic cancer, particularly in terms of metastasis [3].

Cancer is the second leading cause of death worldwide, and ranks next to cardiovascular diseases [4, 5]. Many cancer treatments have been discovered and new compounds are continuously being tested [6, 7]. Various studies have been conducted using heparin and heparin-like molecules, either alone, or in combination with other chemotherapy agents in treatments of different neoplasms [8, 9]. The concept that specific heparin and heparin-like molecules of certain lengths or 3D structures may be required for binding to certain growth factor families

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has become an area of active research in the treatment of cancers [10].

Therefore, the aim of this article is to provide an overview of recent progress on the use of heparin, heparin sulfate, and related synthetic products in cancer treatment, which could represent a major breakthrough in the field of oncology, along with other promising therapeutic uses.

Discussion

Structure and cellular localization of heparin and heparin sulfate

Heparin is a carbohydrate that is part of the glycosaminoglycan family of molecules, which includes a variety of closely related members such as heparin sulfate. There are two types of heparin: unfractionated heparin (UFH) and LMWH. UFH has variable biological activity because of its heterogeneous mixture of linear polysaccharide chains [11]. LMWHs are a diverse group of compounds that are derived from UFH; they were first produced in the late 1970s and early 1980s by the fractionation of crude UFH. Most of them are produced by various chemical or physical depolymerization techniques, while some are produced by enzymatic depolymerization [2]. Because of the differences in the ways they are manufactured, LMWHs are available in a wide range of mean molecular weights and a mix of polysaccharide chain lengths, and the products differ significantly in terms of their pharmacological properties [2].

Heparin sulfate is characterized by a polyanionic linear polysaccharide structure similar to that of heparin, which consists of repeated disaccharide units that can be further modified by processes such as sulfation and deacylation. However, despite their structural similarity, these two molecules differ in terms of both their physiological and pathological functions [12].

Heparin sulfate occurs in the body in the form of heparin sulfate proteoglycans (HSPGs), which can either be anchored to the cell surface or secreted in the extracellular matrix [11]. Heparin sulfate interacts with a wide range of proteins and can affect a great number of vital pathways in the body, including processes such as homeostasis, development, inflammation, and cancer progression. Heparin sulfate is also found in all eukaryotic cells and therefore all cancer cells. The specific role that heparin sulfate plays in cancer pathogenesis, has become the subject of ongoing research today.

Although they are very closely related, heparin and heparin sulfate have some structural differences, particularly in the composition of their sugar chains, and in the degree of sulfation and acetylation [12]. These variations are due to the differences in their biosynthesis in different cells [12]. At least 22 enzymes are involved in the biosynthesis and fine-tuning of these molecules [13]. Both substances are linear polymers consisting of alternate units of α-D-glucosamine (GlcN) and uronic acid, which are present in the form of either β-D-glucuronic acid or α-L-iduronic acid. The units are linked together by (1→4) glycosidic linkages [14]. In heparin sulfate, the GlcN can be either N-sulfated or N-acetylated, whereas in heparin, it is predominantly N-acetylated. In addition, heparin has a higher degree of sulfation (2.3–2.8 sulfates/disaccharide) than heparin sulfate (0.6–1.5 sulfates/disaccharide) [14]. Because of these differences, heparin is more charged than heparin sulfate [14]. The uronic acid in heparin sulfate is mostly in the form of D-glucuronic acid, whereas in heparin, it is predominantly in the form of L-iduronic acid [15]. Heparin sulfate chains (around 30 kDa) are also generally longer than those of heparin (15 kDa) [16].

In addition to their structural differences, heparin and heparin sulfate exhibit differences in their cellular localization. Heparin sulfate is found attached to core proteins in proteoglycans on cell surfaces and within the extracellular matrix of most types of cells and tissues, whereas heparin is stored exclusively in the granules of certain types of mast cells [17].

Function of heparin and heparin sulfate

Heparin is mostly used for its antithrombotic activity [18]. Specifically, it is used in treating and preventing pulmonary emboli, deep vein thrombosis, myocardial infarction, unstable angina, and arterial thromboembolisms [19]. Heparin – and heparin-like molecules – acts by binding to the lysyl residues on antithrombin and accelerating the rate of complex formation.

Shriver et al. reported that the activation of antithrombin leads to coagulation cascade inhibition [15].

A large number of proteins, termed heparin-binding proteins, such as membrane receptors, enzyme inhibitors, chemokines, growth factors, and extracellular matrix proteins, bind to heparin sulfate. In fact, these proteins primarily bind to heparin sulfate rather than heparin itself, and thus “heparin-sulfate-binding proteins” would be a more appropriate term. This binding is mostly based on charge-charge interactions between the basic amino acids of the proteins and the sulfate/carboxylate group of the sugars [20].

Heparin and heparin-like molecules have been found to play a role in a wide variety of cellular functions, and the importance and diversity of their possible uses has only recently begun to be fully recognized. For cancer patients, there is evidence that the use of UFH and LMWH confers a greater survival advantage [21]. Interestingly, there seems to be an important link between thrombosis and cancerous tumors, with the former playing a role in pathogenesis and tumorigenesis. This has led to the investigations of a potential therapeutic use for antithrombotic agents in cancer treatment.

Although the mechanisms underlying the protective function of these agents in cancer remain poorly understood, it has been suggested that they exert their effects through noncoagulation pathways [21]. The suggested mechanisms include the inhibition of proliferation, metastasis, and cell adhesion [21] as well as other processes such as interference with tumor growth factors, multidrug resistance, and thrombin generation.

Because of the wide range of effects associated with heparin sulfate, including effects related to cancer progression, research efforts are being increasingly invested in investigating the possible roles of heparin, heparin sulfate, and other associated molecules, such as sulfated alginates, in the treatment of different cancer types.

Roles of heparin and heparin sulfate in cancer pathogenesis

Angiogenesis

An approach to target cancer is to inhibit the biological processes that drive cell growth [22].

Angiogenesis is a critical process required for the survival, growth, and metastasis of a tumor, and it is regulated by growth factors. One of the types of growth factors that have been shown to play an important role in tumor development and progression are fibroblast growth factors (FGFs) [22]. They exert their effect by binding to their receptors, fibroblast growth factor receptors, which are tyrosine kinase receptors, thereby initiating a signaling cascade. By binding to FGFs, they initiate cascades involving RAS-mitogen-activated protein kinase (MAPK), PI3K-AKT, and PLCγ pathways. These pathways manifest in proliferation/differentiation, increased survival, and changes in morphology for adhesion and migration purposes, respectively [23]. In another example, binding to FGF2 leads to an increase in the expression of anti-apoptotic proteins. A synergistic effect of FGF along with vascular endothelial growth factor (VEGF) has been recently studied and shown to ultimately amplify tumor angiogenesis and growth [24]. Like FGF, the VEGF pathway utilizes the RAS-MAPK and PI3K-AKT pathways for its role in angiogenesis. However, an additional mechanism is also utilized, mainly the SRC-FAK pathway. This later cascade further develops the cell by enhancing the cellular motility.

In a recent study, the movement of FGF was microscopically tracked in mice with a vastly angiogenic tumor in the presence and absence of

heparin. There was a significant difference in the results between the two groups. The group treated with heparin had smaller, pale tumors with decreased angiogenesis, and downstream signaling was inhibited. In contrast, the control group had highly vascularized, massive tumors. This study provided the evidence of the mechanism through which heparin can inhibit tumor growth: sequestration of FGF and the inhibition of its binding to its receptor. The ultimate consequence of such a mechanism is the downregulation of the receptor activity and thus the inhibition of its effects on the progression of a tumor. This activity is attributed to the fact that heparin, by competition, may disrupt the interaction between FGF and heparin sulfate proteoglycans, which normally regulates FGF signaling and cell polarity during cell migration [25].

In another study, similar results were obtained with a variety of LMWHs (i.e., dalteparin, enoxaparin, and tinzaparin). Dalteparin was the most effective of the 3 drugs in minimizing angiogenesis and subsequent tumor growth [2]. As with the previous study, the authors concluded that LMWHs sequester FGFs away from their low-affinity receptors on tumor cells.

In addition to its effects on angiogenesis, heparin has been shown to affect in various tumor formation and progression steps. Several studies have elucidated the mechanisms by which heparin exerts these effects [26].

Cancer cell proliferation

Given that heparin sulfate is an important component of the cell surface of all cells and is found in the extracellular matrix, it is not surprising that it plays several roles in terms of cell division and proliferation. Heparin sulfate can act as either a positive or negative modulator of cell proliferation. It acts through different series of pathways, which ultimately lead to either proliferation (i.e., positive modulation) or the inhibition of division (i.e., negative modulation) [27]. Heparin sulfate's positive modulatory effect can be explained through an example of the FGF pathway. To activate the proliferative pathway, FGF binds to its receptor, which is found on the surface of cells. This binding is mediated by heparin sulfate as it activates the receptor and allows for the binding of the protein to its receptor, which ultimately leads to cell proliferation [27].

Heparin can also help inhibit the proliferation of several cell types. It exerts this antiproliferative effect mainly by inhibiting some proto-oncogenes such as c-myc and c-fos through modifications of the protein kinase C-dependent signal transduction pathway [28]. It was demonstrated that heparin has an inhibitory effect on the phosphorylation (i.e., the activation) of the MAPK, which is part of the signaling cascade of protein kinase C [28]. A study attempted to show that heparin is responsible for the proliferation of some cancer cell lines, such as in colon cancer, but the results were inconclusive [29].

Immune system

Heparin sulfate has been shown to play an important role in the immune system through its ability to bind to a wide range of proteins. It has been shown to regulate a number of immune processes, such as immune system activation, inflammation, leukocyte migration, and leukocyte development. It also plays a number of functional roles that have been heavily studied, as in the functioning of cytokines and chemokines, the sensing of tissue injury, cell adhesion, and being a physical barrier to leukocyte migration.

Heparin also affects the immune system through the inhibition of the complement system and the inhibition of leukocyte activation [30]. This activity could expose cancer cells to the immune system, rendering them more susceptible to immunological attacks [31].

Cancer cell migration and invasion

Heparin sulfate has been found to play a major role in cell migration and invasion. A number of studies have found that the use of heparinase decreases endothelial cell adhesion by up to 40% [32]. The same studies also found that there was an increase in filopodia formation, and thus an increase in endothelial cell migration.

As for heparin, by inhibiting the synthesis of extracellular matrix proteins and inhibiting plasmin (a proteolytic enzyme encoded by the PLG gene), it was shown to affect cancer cell migration and invasion, which are necessary steps for both angiogenesis and metastasis [33].

Use of heparin and heparin sulfate in specific cancer types

As previously stated, heparin has demonstrated some antimetastatic and antitumor effects as part of its anticoagulation activity or through other direct/indirect pathways, such as inhibiting signaling cascades. This causes different effects in different tumor cell lines. Interest in the wide range of chemical properties and mechanisms of action exhibited by heparin and its related products has stimulated research on their effect on breast cancer. Derivatives of heparin have been shown to significantly reduce breast cancer cell proliferation and metastasis both in vitro and in vivo [34]. Their ability to regulate the expression of major extracellular matrix macromolecules suggests that they may be useful in therapeutic targeting [34].

Abu Arab and colleagues reported that LMWH has some inhibitory effect on A495 lung adenocarcinoma cell lines in vitro [35]. They also found that LMWH had a suppressing effect on non-small cell lung cancer cell proliferation, demonstrated by the decreased cell count and diminished expression of c-Myc oncoproteins, which are major proteins involved in multiplication, differentiation, and apoptosis mechanisms. Yu and colleagues showed that when heparin, mainly LMWH, was administered to lung cancer patients as prophylaxis for thrombosis and without other indications for anticoagulants, there was significant and increased survival benefit, particularly in limited-stage small cell lung carcinoma [36].

Heparin-like molecules

In recent decades, a number of derivatives and analogs of heparin and heparin sulfate have been developed from natural sources or chemical synthesis. Sulfated glycosaminoglycans (GAGs) act as analogs of heparin sulfate. Known as heparin sulfate mimetics, they play an important role in some recent advances in the field of cancer therapy.

As mentioned earlier, GAGs are natural heteropolysaccharides that are present in every mammalian tissue. They are composed of repeating disaccharide units that consist of either sulfated or nonsulfated monosaccharides. Their molecular size and the sulfation type vary depending on the tissue, and they exist either as part of the proteoglycan or as free chains. They play important roles in a variety of physiological and pathological conditions.

Alginates are biologically inert, heparin sulfate mimetics that are produced by brown algae (Pheaophyceae) and in certain types of gram-negative bacteria (*Azotobacter* and *Pseudomonas* species) [37]. They are linear polysaccharides that consist of β-D-mannuronic acid (M) and α-L-guluronic acid (G) [37]. By using chemical sulfation to emulate sulfated glycosaminoglycan, alginate is functionalized for further use [37]. Sulfated GAGs are crucial elements of the extracellular matrix. They are involved in a number of different signaling pathways mainly through various interactions with many proteins such as cytokines and growth factors [10].

Specific roles in cancer treatment

Recent studies have shown that an increase in the degree of sulfation on alginates increases the likelihood of binding to FGF-2 [38]. There have also been promising results with regard to growth factor binding of sulfated alginates. In a recent study using submandibular gland oligosaccharides to release growth factors from the cell surface, there was an increased affinity of sulfated GAGs in binding FGF-2 and human growth factor (HGF) [38]. Although much work remains to be done in characterizing the alginates and investigating possible

therapeutic applications of these substances, the early results are promising, particularly in the field of tissue engineering. For instance, the ability of sulfated alginates to sequester growth factors can be used in tissue engineering to inhibit cell growth in diseases such as cancer [10].

In a recent study, sulfated alginates were shown to bind HGF, displacing it from the surface of myeloma cells in a mechanism similar to that of heparin. GAG-bound HGF was released from the surface of human myeloma cells upon treatment with sulfated alginates as well as with heparin. In contrast, no HGF release was observed when non-sulfated alginates were used at any treatment concentration [39].

As mentioned earlier, heparin sulfate GAGs are known to be involved in multiple vital processes such as angiogenesis, adhesion, cell growth, and migration. Thus, it should not be surprising that heparin sulfate mimetics are being synthesized for various pharmacological roles [40]. They have been synthesized using various techniques, and many of the products are still undergoing early clinical evaluation. A major advance in this field was learning that heparin sulfate mimetics can have an important biological antitumor effect in addition to an anti-inflammatory effect. Their antitumor effect is attributed to their heparinase-inhibiting activity [41] as well as other factors. By inhibiting heparinase, the cleavage of heparin sulfate chains and thus their participation in the previously mentioned biological processes can be inhibited. The mechanism of action by which heparin sulfate mimetics inhibit heparinase activity has been described as a competition for the binding of SDf-1/CXCL12 and effects on heparinase expression [42]. A number of promising mimetics have been developed in recent years; their potential roles in cancer therapy are outlined below.

The role of heparin mimetics is not restricted to binding FGF, HGF, and VEGF as has been mentioned previously. As a matter of fact, heparin mimetics have shown to act on multiple factors and to alter several signaling pathways. Some factors worthy of mentioning include Sonic Hedgehog (SHH), Wnt, and EGF-R as these are implicated with multiple types of cancers and their development, progression, and dissemination [43]. For instance, the deregulation of the SHH signaling pathway is a well-known mechanism in the development of cancer. This occurs through the main target genes of this pathway such as PTCH and Gli [44]. Similarly, Wnt and EGF-R have been shown to enhance the invasion and metastasis of malignant cells [45].

Thus, what is promising about some heparin mimetics, is their potential of interfering and inhibiting such aberrant signaling pathways and consequently leading to better outcomes in cancer treatment.

Roneparstat (Table 1 and Fig. 1), which is also known as, SST0001, is a chemically modified nonanticoagulant heparin that has recently been studied for its potential antitumor effects. In preclinical studies on multiple myeloma cell lines in vivo, SST0001 was shown to have an anti-heparinase activity that ultimately resulted in reduced angiogenesis and reduced expression of growth factors (VEGF, HGF, and MMP-9) as well as diminished shedding of promoters of multiple myeloma growth such as heparin sulfate glycoproteins, more precisely termed syndecan-1 [46]. In addition to its antiheparinase activity, SST0001 administration was shown to have a role in the reduction of phosphorylation of several receptor tyrosine kinases such as EGFR, ERBB4, INSR, and IGF1R.

However, phase l clinical studies concerning Roneparstat showed little efficacy in the treatment of multiple myeloma on its own. Heparinase inhibition and their mechanism of action has no direct tumor cell killing function [46]. As such, no significant results were shown that link Roneparstat use to direct antimyeloma effects. However, when combined with bortezomib or melphalan, SST0001's role in heparanase inhibition of multiple myeloma is improved [47]. Thus, the effect of Roneparstat in combination regimens for treating multiple myeloma could be an alternative design to be studied further.

In contrast, in 2016, the development of a potential anticancer drug called Necuparanib (Table 1 and Fig. 1) was discontinued in phase 2 because of a lack of evidence of efficacy, despite having good preclinical indicators.

Necuparanib, known as M402, is a heparin sulfate mimetic that targets tumor compartments in pancreatic cancer. The rationale for its use in cancer treatment was that it mimics HSPGs by sequestering different heparin-binding growth factors and thus modulating several elements of the tumor microenvironment; it has specifically been shown to modulate the factor P-Selectin, which is a cell adhesion molecule on the surface of activated endothelial cells. In fact, the inhibition of the P-Selectin factor can attenuate metastasis and tumor progression by inhibiting tumor cell interaction with the vascular endothelium, which is considered a crucial step in the dissemination of cancer [48]. In another study, M402 has shown to inhibit SHH signaling by specific binding to its transcription factor, Gli [49]. Although it did not result in toxicities, its efficacy was questionable as 57 out of the 120 participants in phase 2 trials died [50].

Another drug, named PI-88 (Table 1 and Fig. 1), is under study in preclinical trials mainly for the treatment of HCC. Recent data have

Table 1
Heparin mimetics currently in clinical trial for use in cancer treatment.

Mimetic	Latest Phase Of Clinical Trial	Target Molecules	Main Type of Cancer Targeted	Primary Results
Roneparstat (SST0001)	I	EGF-R ERBB4 FGF Fibronectin HGF IGF MMP-9 PDGF VEGF	Multiple Myeloma	Little efficacy. No potential of direct antimyeloma effect.
Necuparanib (M402)	I/II	FGF HGF P-Selectin SDF-1α SHH VEGF	Pancreatic Cancer	Multitargeting therapeutic with in vitro and in vivo antiinvasive and antimetastatic activity. Failed phase 2 clinical trial despite having good preclinical indicators
Muparfostat (PI-88)	III	FGF-2 VEGF	Hepatocellular Carcinoma	Positive protective effect in subgroup patients with microvascular invasion. Significant prolongation in disease-free time after the completion of the 1-year treatment. Phase III clinical trials failed to reach the primary disease-free survival endpoint.
Pixatimod (PG545)	I	Cyclin D1 MMP-7 VEGF Wnt/β-catenin	Solid Tumors	Tolerable safety profile, proportional pharmacokinetics, evidence of immune cell stimulation, and disease control in some subjects.

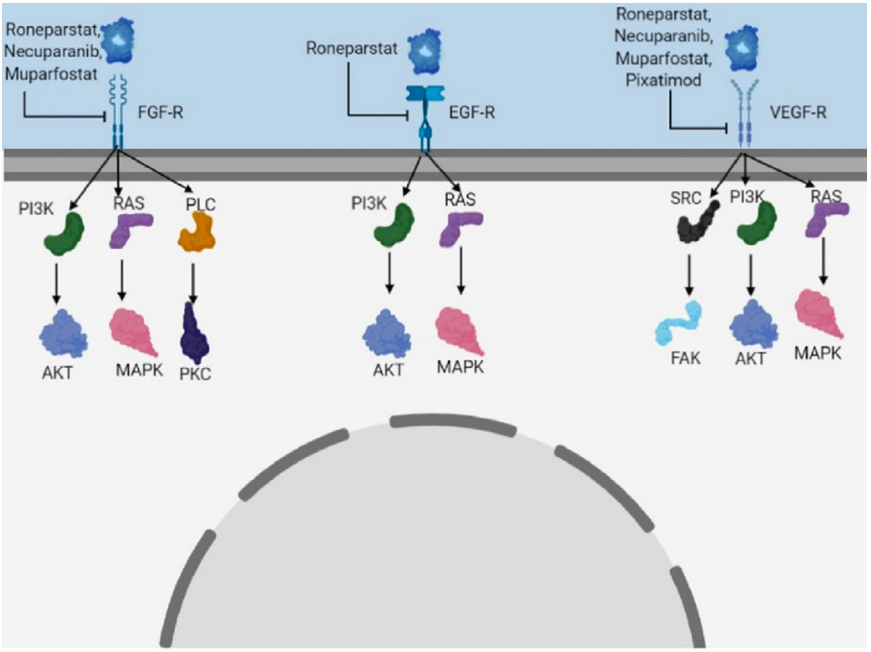

Fig. 1. The Main Signaling Pathways Used by Heparin Mimetics in Cancer Treatment. Figure Legend: FGF-R: Fibroblast Growth Factor Receptor, EGF-R: Endothelial Growth Factor Receptor, VEGF-R: Vascular Endothelial growth factor receptor, AKT: Protein Kinase B, PI3K: Phosphoinositide 3-kinases, PLC: Phospholipase C, MAPK: mitogen-activated protein kinase, PKC: Protein Kinase C, SRC: Proto-oncogene tyrosine-protein kinase, and FAK: Focal adhesion kinase.

suggested a promising role for PI-88 in inhibiting hepatocellular cancer in patients who have undergone hepatectomy [51]. It is believed to produce this effect through antimetastatic and antiangiogenic activities. As with the drugs mentioned above, PI-88, through its antiheparinase activity, has been shown to inhibit angiogenesis in multiple solid tumors such as colon, breast, lung, and hepatocellular cancer through its antiheparinase activity [52]. Another mechanism enabling such a biological effect is the blockage of the interactions of angiogenic growth factors, such as FGF-2 and VEGF, and their receptors with heparin sulfate [53]. PI-88 is currently being evaluated in a phase 3 trial, and is being considered for routine clinical use. However, Phase III clinical trials for HCC failed to reach the primary disease-free survival endpoint [54].

Moreover, its use is associated with some common adverse effects, such as thrombosis, thrombocytopenia, and other effects, mainly related to bleeding.

Another promising heparin sulfate mimetic is PG545. It belongs to a group of heparin sulfate mimetics that are second-generation versions of PI-88. It has been shown to interfere with different steps of tumor development. Similar to other heparin sulfate mimetics, PG545 interferes with angiogenesis through growth factor binding and with metastasis through its antiheparinase activity. More specifically, PG545 was shown to exert its activity on the Wnt pathway in pancreatic ductal adenocarcinoma. It should be noted that the Wnt/β-catenin pathway has a major implication in pancreatic cancer progression by regulating cell cycle progression, apoptosis, angiogenesis, and several other critical steps [55]. Therefore, by directly interacting with Wnt3a and Wnt7a, PG545 inhibits Wnt/β-catenin signaling ultimately leading to the inhibition of proliferation in pancreatic tumor cells. In addition to Wnt3a and Wnt7a, PG545 treatment has shown to decrease the levels of β-catenin and consequently its downstream targets, MMP-7, VEGF, and Cyclin D1, further supporting its antitumor function [56].

It has also been shown to play an important role in reducing the formation of lung metastases in mice that had the resection of their primary tumors (i.e., mastectomy) [57]. PG545's efficacy has shown promising results with solid tumors such as melanoma, breast, liver, colon, and pancreas [58]. It is currently being evaluated in a phase 1 clinical trial for advanced solid tumors.

Other heparin mimetics are also being studied for potential antitumor and antimetastasis effects, but their structure is yet to be disclosed. Worthy of mentioning is the EP80061, which is the lead compound in "small glycol" drugs, as well as an octasaccharide-based heparin mimetic assembled from three different disaccharide units.

Heparanase remains a useful therapeutic target against metastases of cancer. It has been shown to have a catalytic cleft that is suitable for small molecule drug development. Moreover, two proteins, Hpa2 and T5 heparanase, have been shown be a reflection of activated heparanase and its expression level in a tumor microenvironment [59]. These two proteins represent heparanase's nonenzymatic activities in tumor progression and are likely to affect antiheparanase drugs' efficacy. Further studies on targeting the nonenzymatic activity of heparanase should provide the focus of alternative drug development [59]. Thus, developing a drug that would target the catalytic cleft as well as the heparin-binding domain may provide better coverage for both, the enzymatic and nonenzymatic activity of heparanase.

These examples and more show the importance of increasing the amounts of research in the oncology field, as well as other fields, to try and alleviate the global burden of cancer.

Heparin and heparin-like mimetics with chemotherapy

Heparin and Heparin-like mimetics have been used alone and in combination with other chemotherapeutic agents. There have been a mix of results regarding the combination of heparin and heparin-like mimetics with other treatment drugs. One study which compared the combination of cisplatin and LMWH to cisplatin alone on a patient with resected non-small cell lung cancer showed no improved survival between the two arms [60]. On the other hand, another study demonstrated that the use of heparin in combination with chemotherapy significantly decreases chemotherapy-induced coagulopathies and plays a protective role, which eventually caused increased survival in patients [9]. Thus, there is a need for more trials and research on the use of combination treatment modalities to fully understand the mechanisms at work and figure out whether such combinations do really have a benefit for cancer patients.

Potential downfalls

As with any other possible treatments, heparin and heparin-like molecules have their shortcomings. Various studies have shown that the use of these molecules does not bear an increased mean survival or improved clinical outcomes in factors such as disease progression or

metastasis [61]. Adverse effects such as thrombocytopenia, increased risk of thrombosis, abdominal pain, increased fatigue, and general health deterioration may raise concerns for researchers attempting to study these molecules in vulnerable cancer patients as well as concerns from the patients themselves [46]. In addition, clinical trials being conducted using heparin and heparin-like molecules are using relatively small population sizes [62]. This could mean that positive results from said trials might not be representative of entire cancer population groups.

Therefore, although promising results are linked to heparin mimetics in treating malignancy such as recent preclinical tests in many cancers (e.g., breast cancer and mesothelioma), difficulties are being encountered in clinical trials such that a large number of these clinical trials have not shown any evidence to support these promises.

The reason behind some of these disappointing clinical trials remains unclear; however, issues of avoiding adverse side effects while maintaining good bioavailability of heparin mimetics could provide an explanation [63]. Heparin mimetics have shown to have inherent heterogeneity and affinity toward multiple targets, thus exacerbating adverse effects. Another reason could be that clinical trials conducted so far include patient populations too diverse in their disease, thus, interfering with overall response [63]. In addition, the antiheparanase drugs currently under development predominantly focus on the inhibition of enzymatic activity of heparanase disregarding its nonenzymatic activity [59]. This raises concerns for possible alternative designs, possibly involving mimetics with a combination of other drugs.

Conclusion

Today, over 50 clinical trials have focused on the use of heparin and heparin-like molecules in cancer treatment. Some evidence has shown that these molecules interfere with certain steps of cancer development by halting the progression of different tumors and increasing mean survival. Because of these positive outcomes, some heparin mimetics have reached final stages of clinical trials for the treatment of different cancer types.

However, there still remains conflicting results in terms of the overall beneficial nature of these drugs. These mixed results imply that more research is needed to fully understand the true effects of these treatment modalities on cancer patients.

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Author contributions

J.A. and H.H.K. Drafted the original manuscript. J.A., H.H.K, J.B. and H.A. Revised and edited the draft. J.A. and H.H.K. were responsible for article curation and investigation. H.A. supervised and validated the final product. All authors gave final approval of this version to be published and agreed to be guarantor of the work.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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