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General review

Heparin beyond anti-coagulation

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ABSTRACT

Heparin has served as a mainstream anticoagulant for over eight decades. Clinically heparin-derived compounds significantly contribute to prevention and treatment of thrombotic events complicated in numerous medical conditions such as venous thromboembolism, coronary artery disease and extracorporeal circulation processes. Moreover in recent years, various off-labeled efficacious potentials of heparin beyond anti-coagulation are dramatically emerging, and increasingly investigated in clinical studies. Herein this article presents a comprehensive update on the expanded applications of heparin agents, covering the pregnant clinic, respiratory inflammation, renal disease, sepsis, pancreatitis, among others. It aims to maximize the beneficial profile of a pharmaceutical product through medical re-purposing development, exemplified by heparin, to address the unmet clinical needs of severe illness including coronavirus disease 2019 (COVID-19).

Introduction

Representing an outstanding group of naturally generated polysaccharide, heparin was termed due to its original isolation from liver tissue one century ago. To date, heparin has been serving as a mainstream anticoagulant medicine in the clinical practice for eight decades since the first human application against thrombotic disorders [1, 2]. Biochemically, the fundamental structure of heparin consists of repeating disaccharide units of uronic acids (L-iduronic or D-glucuronic acid) and *N*-acetyl-D-glucosamine [3]. Depending on a contained unique pentasaccharide sequence, heparin exerts anticoagulant activity upon binding with antithrombin, in turn to suppress activation of factor Xa and IIa in the coagulation cascade [1, 3].

The discovery and clinical application of heparin have significantly improved the outcomes in numerous aspects of serious medical conditions. In this light, several heparin-based agents, such as unfractionated heparin (UFH) and low molecular weight heparin (LMWH), are included in World Health Organization's (WHO) List of Essential Medicines [4]. UFH is the preliminary product usually processed from porcine or bovine intestine tissues in pharmaceutic industry, and has various molecular lengths ranging from 2000 up to 40,000 Dalton (Da). On the other hand, with molecular weights below 7000 Da LMWH compounds are derived from UFH through depolymerization reactions facilitated by certain chemical and enzymatic reagents [1, 4]. Pharmacologically, LMWH medications have better bio-availability, higher anti-factor Xa/IIa activity ratios, and minimized risks of hemorrhage and heparin-induced thrombocytopenia (HIT), compared to those of UFH [4–6].

As a classic anticoagulant, heparin family drugs are typically utilized to prevent or to treat thrombotic pathogenesis-linked medical conditions such as pulmonary embolism, coronary artery disease, and potential clotting events in hemodialysis for renal failure [1, 7]. Additionally, heparin represents a widely used surface coating agent to improve blood compatibility of numerous medical devices including cardiopulmonary bypass, extracorporeal circulation, vascular stent, among others [8]. Interestingly in recent years, heparin treatment is going beyond these traditional indications and entering into a broad spectrum of expanded clinical fields, inspired by the insights from advanced polysaccharide science and contemporary disease biology [1, 4, 9]. Herein, this article thus highlights an emerging profile of novel medical applications for heparin-based medications (Table 1).

The pregnant clinic

It has been recently noted that, in addition to the well-known anticoagulant efficacy, heparin can also orchestrate an extra-array of biological effects including anti-inflammation/anti-complement, vascular endothelial protection, trophoblast promotion and apoptotic inhibition [9, 10]. As such, this functional profile appears helpful for certain obstetric patients to improve the clinical outcomes through alleviating the hyper-coagulant state, modulating micro-vascular/placental biology, among other modes [10]. To date while the expanded indications in this perspective are yet to be corroborated by relevant large-scale clinical trials for regulatory approval in terms of the drug labeling update, there has been a professional consensus that heparin agents can be used as an empirical approach to treat or prevent early pregnancy complications such as spontaneous abortion [10, 11]. In this regard, prophylactic management with LMWH of

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Table 1
Updated application profile of heparin products.

Mode	Medical usage	References
Anticoagulant	Deep vein thromboembolism	[1, 3]
	Unstable coronary artery disease	[1, 3]
	Extracorporeal circulation processes	[4, 7]
	Thromboprophylaxis in perioperative period	[1, 4]
	Medical device intervention	[4, 8]
	Coating of bio-materials contacting blood	[8]
Comprehensive	Spontaneous abortion	[10, 11]
	Chronic obstructive pulmonary disease	[16, 17]
	Diabetic nephropathy/nephrotic syndrome	[20, 21]
	Sepsis/severe COVID19	[26, 30]
	Pancreatitis	[31, 32]
	Burning wound (topic use)	[48]

standardized dosage until abortion or delivery has been demonstrated to significantly raise the live-birth rates (by 20%~30%) in patients suffering from recurrent miscarriage, and particularly in the cases with antiphospholipid antibody or methylenetetrahydrofolate reductase gene polymorphisms [11, 12]. Moreover, LMWH was also revealed to dramatically improve pregnancy events and live-birth rates upon in vitro fertilization (IVF) in women with recurrent implantation failure and thrombophilic disorders [13]. In these scenarios, the underlying comprehensive mechanisms included preventing microthromboses, facilitating trophoblast differentiation/migration, and up-regulating the level of free insulin-like growth factor [14].

Chronic respiratory inflammation

Heparin medicine can confer certain anti-inflammatory effects through several mechanisms of actions such as regulating cytokine/chemokine expression, suppressing immune cell infiltration and particularly minimizing obstructive mucous secretion [3, 15]. These inflammatory-modulating roles of heparin in synergy with its anticoagulant activity thus come up with an exceptional set of therapeutic potentials for managing chronic obstructive pulmonary disease (COPD). In this light, adding LMWH to the existing treatment was revealed to improve blood coagulation parameters of patients with COPD, including elongated prothrombin time (PT)/activated partial thromboplastin time (APTT) and reduced blood viscosity/D-dimer/fibrinogen levels, compared to those of the subjects on conventional therapy only. Meanwhile, these combined medications were able to result in higher forced expiratory volume in 1 s/forced vital capacity (FEV1/FVC), oxygen saturation of blood (SaO2), and lower partial pressure of carbon dioxide (PaCO2) [16, 17]. On the other hand, it has been noted that inhaled heparin or its derivatives confer the therapeutic efficacy of relieving respiratory hyper-reactivity disorders such as asthma, through diminishing histamine and leukotriene-induced bronchial constriction [9, 15]. Moreover, LMWH was discovered to be capable of down-regulating the release of interlukine (IL)-4, IL-5, IL-13 and tumor necrosis factor (TNF)-α from the peripheral blood mononuclear cells (PBMCs) of asthmatic patients [18]. Thus, it is conceivable that pulmonary medicine can evolve with including heparin agents to circumvent hyper-coagulation and inflammation.

Renal disease

Physiologically, the glomerular capillary filtration membrane controls the macro-molecule filtration based upon molecular weight, charge, and shape; in consistent, the ionic charge of the glomerular basement membrane (GBM) is characterized by containing highly sulfated glycosaminoglycan heparan (SGH) [19]. Diminished SGH in GBM due to up-regulated heparanase in certain renal pathology is prone to increase permeability to negatively charged macromolecules such as albumin, consequently resulting in proteinuria [9, 19]. Interestingly it has been proposed that LMWH may serve as an in vivo heparanase inhibitor to restore CSH dominance in GBM, thus alleviating the leaking of plasma protein into urine. In this regard without affecting hemodynamic physiology, enoxaparin and an oral LMWH (sulodexide) were revealed to significantly minimize the severity of proteinuria in the patients with diabetic nephropathy, but not in glomerulonephritis [19, 20]. Likewise, LMWH was noted capable of facilitating clinical remission of patients with steroid-sensitive nephrotic syndrome through significant reducing proteinuria, urinary glycosaminoglycans and nephrotic periods [21, 22]. Regarding the therapeutic mechanisms in this case, besides the above heparanase inhibitory mode, another possibility is suppressing the hyper-active elastase which can degrade subendothelial matrix thus causing glomerular damage and proteinuria [21]. Of note, whereas with an improved profile of adverse reaction LMWH has been more popularly utilized in managing relevant medical conditions recently, UFH is still preferred in patients with renal failure due to its shorter half life time and better reversibility by protamine for minimizing potential drug-accumulated toxicities [3, 23].

Sepsis

With the high mortality, sepsis remains a critical medical condition that needs intensive care. Although antibiotic agents serve as an efficacious means for controlling the etiological microorganisms, an official strategy of managing the induced patho-physiology during sepsis, septic shock in particular, is yet to be established [24, 25]. Anyhow in regard to the core pathogenesis, it has been recognized that the interactions between inflammatory factors and endothelial injury activate the coagulating cascade to form micro-thrombosis, consequently resulting in organ damages [24]. As such to cope with this comprehensive challenge, heparin is emerging as an attractive medicine owing to the functional profile of pleiotropic effects about clotting inhibition, endothelial protection and immune modulation [3, 9]. In corollary through a multi-center retrospective clinical investigation, heparin was utilized to be an effective adjuvant therapy for sepsis and significantly diminished the mortality in a subset of patients with disseminated intravascular coagulation (DIC) dynamically over 3 months following the treatment [25]. Consistently in parallel, controlled clinical trials of anticoagulant versus placebo demonstrated that prophylactic treatment with UFH or LMWH (up to 15,000 units/day, intravenously) significantly reduced 28-day mortality (from 38% to 30%) in the patients with sepsis or severe sepsis [26]. Moreover, while conferring a better survival benefit and improving coagulant parameters for the patients with sepsis, heparin was also noted to restore the protective proteoglycans on endothelial surface, and to down-regulate the levels of serum inflammatory cytokines such as IL-6 as well as TNF-α [24,27,28] Additionally, sepsis was observed to be the most frequent complication in patients with coronavirus disease 2019 (COVID-19), of which aberrant coagulating function such as elevated D-dimer was noted as one of the risk factors for poor prognosis [29]. Impressively, treatment with LMWH appeared to improve the clinical outcomes of COVID-19 patients, upon down-regulation of D-dimer level and improvement of the immune profile [30].

Pancreatitis

As a complicated inflammatory condition, acute pancreatitis (AP) presents various degrees of clinical severity, and severe AP is associated high mortality due to systemic pathology without specific treatments. While AP pathogenesis is yet to be well delineated, the comprehensive interactions has been noted between inflammatory factors, pro-coagulant pathways and vascular endothelial injury [31, 32]. To cope with these multidimensional challenges, the functional

profile of heparin can in this case confer an exceptional set of therapeutic efficacy covering anti-inflammation, anti-coagulation and endothelial protection [4, 9, 31]. In particular, heparin also contributes to suppressing activity of digestive enzymes (trypsin and chymotrypsin), an additional key mediator in early AP pathogenesis [31]. Clinically in corollary, LMWH has been demonstrated to significantly improve the prognosis of severe AP without increasing bleeding events, including reducing hospital stay, mortality and systemic complications [32, 33]. Of note, LMWH strikingly diminished pancreatic necrosis development to 3.1% from 22.6% of the patients, which represents a phenotype of organ damages resulting from TNF-α. Besides, heparin in synergy with insulin is particularly efficacious on managing hypertriglyceridemia-induced AP, since heparin binds with lipoprotein lipase (LPL) and releases LPL from tissues into the blood to catabolize circulating triglycerides [34, 35].

Cancer

Neoplastic disorders are known to be epidemiologically associated with a higher co-morbidity of venous thromboembolism (VTE). The incidence of VTE is elevated by up to 6 fold in patients with cancer compared to those without tumor, and vice versa oncologic patients represent approximately 20% VTE cases newly diagnosed [36]. In terms of pathogenesis, cancer-linked hyper-coagulating state appears directly resulting from up-regulated tissue factor expression which thus leads to constitutive activation of the extrinsic coagulant pathway. Meanwhile, development of cancer-associated VTE can also be indirectly facilitated by several systemic factors including platelet/endothelial activation and pro-inflammatory cytokines [36–38]. Interestingly, while serving as an well-established anti-coagulant medication for preventing and managing cancer-associated VTE, heparin has been proposed to potentially go beyond this aspect and to exert certain anti-neoplasm effects through inhibiting angiogenesis, metastasis and P-glycoprotein-mediated drug resistance [3, 4]. Nevertheless, the results of clinical studies with heparin regarding therapeutic efficacy against malignancies have so far been controversial. Although LMWH was revealed to significantly improve overall survival (OS) of 1 and 2 years in neoplastic patients with chemotherapy [39], a prophylactic investigation showed that adding dalteparin to the standard therapy did not confer a survival benefit to lung cancer patients [3]. Anyhow, there is a medical consensus of using anti-coagulant medications to minimize the morbidity of cancer-associated VTE [4, 39].

Thrombotic disorders during cancer progressing result from not only neoplastic pathogenesis-associated coagulating pathways, but also the oncologic medications including chemotherapy, hormonal treatment, and targeted drugs implicating both small chemical compounds and monoclonal antibodies [37, 40, 41]. Recently with the clinical advantages of non-painful administration and improved therapeutic window novel oral anticoagulants (NOACs) such as apixaban and dabigatran are emerging as an attractive wave of pharmaceutical options for managing hyper-coagulant pathology [41, 42]. Whereas emerging oral anticoagulants are increasingly utilized to prevent and to treat thrombotic disorders including cancer-associated VTE in numerous clinical settings, elevated bleeding events of NOACs (1.904-fold higher hazard ratio) have been noted versus those of LMWH particularly in patients with digestive tract tumors [42]. It thus appears that heparin agents should still be chosen over NOACs for anticoagulant intervention in cases of gastrointestinal neoplasm [42, 43]. Besides, NOACs are known to be the substrates of cytochrome P450 C3A4 and P- glycoprotein (P- gp) which significantly contribute to the processing trajectory of pharmacokinetics [43, 44]. Of note, numerous oncologic medications including cytotoxic and targeted compounds have been revealed to either induce or inhibit C3A4 and P-gp [43, 45], raising a challenging issue of drug-drug interactions (DDI) to consequently affect efficacy and safety of NOACs in the clinic. It is thus plausible that heparin agents represent better options than NOACs for anticoagulant intervention in cancer patients with anti-neoplastic medications, in regard of the minimized DDI. As such, the relevant professional organizations including the American Society of Clinical Oncology and the European Society of Medical Oncology have recommended parenteral anticoagulants to be the first-line medications for the treatment and prevention of VTE in patients with active cancer, whereas NOACs can be considered for early maintenance and long-term therapy in patients with VTE and stable neoplasms being not on anticancer drugs [46].

Perspective

Since being discovered as a naturally-derived polysaccharide compound, heparin has gone through a long journey of life-saving for eight decades, principally serving the anticoagulant purpose in most medical fields [1, 3]. Beyond anti-coagulation in recent years, medications of heparin family are noted to confer a broad variety of therapeutic effects systemically on abortion, sepsis, certain types of inflammation in several organs, among others [4, 15]. Meanwhile, heparin agents can also substantially contribute to local lesion treatment of the patients, including intra-cameral infusion to minimize the inflammatory response upon cataract surgery [47], and tissue irrigation of superficial skin burns to improve the wound healing parameters [48]. Additionally in interest of medical device practice, a heparin-coated extracorporeal circulating system was noted to down-regulate the inflammatory signs and bio-markers following cardiopulmonary bypass surgery [49]. In relevance, the heparin-coated ventricular implanting materials were revealed to diminish the risk of HIT comparing to those with systemic heparin application [50]. Impressively, an *ex vivo* blood cleaning device containing heparin- attached polyethylene beads has just been approved to remove the pathogen and inflammatory cytokines from the blood circulation of patients with COVID-19 [51].

While contemporary clinical studies have revealed a greater picture regarding the therapeutic potentials of existing heparin medications beyond anti-coagulation, the fundamental innovation of structure-activity relationship is raising a wave of various heparin-like compounds with diminished anticoagulant function to exert novel biologic effects. Of note, these non-anticoagulant heparin analogues can confer an optimized therapeutic window, particularly in the medical situations for which anti-coagulation is not needed [4, 9]. Interestingly in this regard, certain naturally derived heparin analogues were identified to be capable of inhibiting crucial pathogenesis pathways of major neuro-degenerative disorders such as Alzheimer's and Parkinson's diseases [4, 52]. Furthermore, several non-anticoagulant heparin derivatives resulting from the structural modifications have come up with the encouraging performance in clinical studies [9, 53]; for instance, the 2-O, 3-O desulfated heparin CX-01 has been demonstrated to enhance the complete remission and hematological recovery of acute myeloid leukemia with chemotherapy upon suppressing CXC chemokine CXCL12-mediated cell sequestration within marrow in a pilot clinical investigation [54]; in parallel, the N-acylated glyco-split heparin SST0001(Roneparstat) was identified as a potent inhibitor for heparanase and receptor tyrosine kinases, thus to confer notable benefits of stable disease to advanced multiple myeloma in a phase I clinical trial [53, 55]. Hence, deciphering the iceberg of heparin biology and chemistry has just advanced beneath the surface of water, where novel therapeutic potentials are yet to be translated from the cutting-edge scientific discoveries.

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References

[1]] Hemker HC. A century for heparin: past, present and future. J Thromb Haemost 2016;14:2329–38.
[2] Barrowcliffe TW. History of heparin. Handb Exp Pharmacol 2012;217:3–22.
[3] Oduah EI, Linhardt RJ, Sharfstein ST. Heparin: past, present, and future. Pharmaceuticals 2016;9:38.
[4] Lima M, Rudd T, Yates E. New applications of heparin and other glycosaminoglycans. Molrcules 2017;22:749.
[5] Arepally GM. Heparin-induced thrombocytopenia. Blood 2017;129:2864–72.
[6] Chen D, Qi EY. Innovative highlights of clinical drug trial design. Transl Res 2020;224:71–7.
[7] Lazrak HH, René É, Elftouh N, et al. Safety of low-molecular-weight heparin compared to unfractionated heparin in hemodialysis: a systematic review and meta-analysis. BMC Nephrol 2017;18:187.
[8] Biran R, Pond D. Heparin coatings for improving blood compatibility of medical devices. Adv Drug Deliv Rev 2017;112:12–23.
[9] Cassinelli G, Naggi A. Old and new applications of non-anticoagulant heparin. Int J Cardiol 2016;212(Suppl 1):S14–21.
[10] Yuksel H, Kayatas S, Boza AT, et al. Low molecular weight heparin use in unexplained recurrent miscarriage. Pak J Med Sci 2014;30:1232–7.
[11] Eid MI, Abdelhafez MS, El-Refaie W, et al. Timing of initiation of low-molecular-weight heparin administration in pregnant women with antiphospholipid syndrome: a randomized clinical trial of efficacy and safety. Int J Womens Health 2019;11:41–7.
[12] Cetin O, Karaman E, Cim N, et al. The impact of low molecular weight heparin on obstetric outcomes among unexplained recurrent miscarriages complicated with methylenetetrahydrofolate reductase gene polymorphism. Ginekol Pol 2017;88:260–5.
[13] Potdar N, Gelbaya TA, Konje JC, et al. Adjunct low-molecular-weight heparin to improve live birth rate after recurrent implantation failure: a systematic review and meta-analysis. Hum Reprod Update 2013;19:674–84.
[14] Dentali F, Grandone E, Rezoagli E, et al. Efficacy of low molecular weight heparin in patients undergoing in vitro fertilization or intracytoplasmic sperm injection. J Thromb Haemost 2011;9:2503–6.
[15] Mousavi S, Moradi M, Khorshidahmad T, et al. Anti-inflammatory effects of heparin and its derivatives: a systematic review. Adv Pharmacol Sci 2015;2015:507151.
[16] Shi X, Li H. Anticoagulation therapy in patients with chronic obstructive pulmonary disease in the acute exacerbation stage. Exp Ther Med 2013;5:1367–70.
[17] Song YJ, Zhou ZH, Liu YK, et al. Prothrombotic state in senile patients with acute exacerbations of chronic obstructive pulmonary disease combined with respiratory failure. Exp Ther Med 2013;5:1184–8.
[18] Shastri MD, Stewart N, Eapen M, et al. Opposing effects of low molecular weight heparins on the release of inflammatory cytokines from peripheral blood mononuclear cells of asthmatics. PLoS ONE 2015;10:e0118798.
[19] Lewis EJ, Xu X. Abnormal glomerular permeability characteristics in diabetic nephropathy: implications for the therapeutic use of low-molecular weight heparin. Diabetes Care 2008;31(Suppl 2):S202–7.
[20] Benck U, Haeckel S, Clorius JH, et al. Proteinuria-lowering effect of heparin therapy in diabetic nephropathy without affecting the renin-angiotensin-aldosterone system. Clin J Am Soc Nephrol 2007;2:58–67.
[21] Zhai S, Hu L, Zhong L, et al. Low molecular weight heparin may benefit nephrotic remission in steroidsensitive nephrotic syndrome via inhibiting elastase. Mol Med Rep 2017;16:8613–8.
[22] Akimoto T, Yamazaki T, Kusano E, et al. Therapeutic Dilemmas regarding anticoagulation: an experience in a patient with nephrotic syndrome, pulmonary embolism, and traumatic brain injury. Clin Med Insights Case Rep 2016;9:103–7.
[23] Atiq F, van den Bemt PM, Leebeek FW, et al. A systematic review on the accumulation of prophylactic dosages of low-molecular-weight heparins (LMWHs) in patients with renal insufficiency. Eur J Clin Pharmacol 2015;71:921–9.
[24] Li X, Ma X. The role of heparin in sepsis: much more than just an anticoagulant. Br J Haematol 2017;179:389–98.
[25] Yamakawa K, Umemura Y, Hayakawa M, et al. Benefit profile of anticoagulant therapy in sepsis: a nationwide multicentre registry in Japan. Crit Care 2016;20:229.
[26] Wang C, Chi C, Guo L, et al. Heparin therapy reduces 28-day mortality in adult severe sepsis patients: a systematic review and meta-analysis. Crit Care 2014;18:563.
[27] Fan Y, Jiang M, Gong D, et al. Efficacy and safety of low-molecular-weight heparin in patients with sepsis: a meta-analysis of randomized controlled trials. Sci Rep 2016;6:25984.
[28] Chen D. Dual targeting autoimmunity and cancer: from biology to medicine. J Clin Pharmacol 2018;558:990–6.
[29] Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 2020 pii: S0140-6736(20)30566-3.
[30] Lin L, Lu L, Cao W, et al. Hypothesis for potential pathogenesis of SARS-CoV-2 infection—a review of immune changes in patients with viral pneumonia. Emerg Microbes Infect 2020. doi: 10.1080/2222175.
[31] Dumnicka P, Maduzia D, Ceranowicz P, et al. The interplay between inflammation, coagulation and endothelial injury in the early phase of acute pancreatitis: clinical implications. Int J Mol Sci 2017;18:E354.
[32] Tozlu M, Kayar Y, İnce AT, et al. Low molecular weight heparin treatment of acute moderate and severe pancreatitis: a randomized, controlled,open-label study. Turk J Gastroenterol 2019;30:81–7.
[33] Qiu Q, Li GJ, Tang L, et al. The efficacy of low molecular weight heparin in severe acute pancreatitis: a systematic review and meta-analysis of randomized controlled trials. J Dig Dis 2019;20:512–22.
[34] Aryal MR, Mainali NR, Gupta S, et al. Acute pancreatitis owing to very high triglyceride levels treated with insulin and heparin infusion. BMJ Case Rep 2013;2013 pii: bcr2013008550.
[35] Hammond DA, Finlay L. Treatment of hypertriglyceridemia-induced acute pancreatitis with insulin, heparin, and gemfibrozil: a case series. Hosp Pharm 2017;52:675–8.
[36] Donnellan E, Kevane B, Bird BR, et al. Cancer and venous thromboembolic disease: from molecular mechanisms to clinical management. Curr Oncol 2014;21:134–43.
[37] Donnellan E, Khorana AA. Cancer and venous thromboembolic disease: a review. Oncologist 2017;22:199–207.
[38] Chen D, Goswami CP, Burnett RM, et al. Cancer affects microRNA expression, release, and function in cardiac and skeletal muscle. Cancer Res 2014;74:4270–81.
[39] Liu ZL, Wang Q, Wang M, et al. Low molecular weight heparin in treating patients with lung cancer received chemotherapy: a meta-analysis. J Cancer Res Ther 2018;14(Supplement):S437–43.
[40] Nasser NJ, Fox J, Agbarya A. Potential mechanisms of cancer-related hypercoagulability. Cancers (Basel) 2020;12(3) pii: E566.
[41] Kunimasa K, Nishino K, Kimura M, et al. Pembrolizumab-induced acute thrombosis: a case report. Medicine (Baltimore) 2018;97:e10772.
[42] Lee JH, Oh YM, Lee SD, et al. Rivaroxaban versus low-molecular-weight heparin for venous thromboembolism in gastrointestinal and pancreatobiliary cancer. J Korean Med Sci 2019;34(21):e160.
[43] Moik F, Pabinger I, Ay C. How I treat cancer-associated thrombosis. ESMO Open 2020;5(1) pii: e000610.
[44] Farge D, Frere C. Recent advances in the treatment and prevention of venous thromboembolism in cancer patients: role of the direct oral anticoagulants and their unique challenges. F1000Res 2019;8 pii: F1000 Faculty Rev-974.
[45] Chen DH, Zhang XS. Targeted therapy: resistance and re-sensitization. Chin J Cancer 2015;34:496–501.
[46] Ay C, Kamphuisen PW, Agnelli G. Antithrombotic therapy for prophylaxis and treatment of venous thromboembolism in patients with cancer: review of the literature on current practice and emerging options. ESMO Open 2017;2:e000188.
[47] Caca I, Sahin A, Cingu AK, et al. Effect of low molecular weight heparin (enoxaparin) on congenital cataract surgery. Int J Ophthalmol 2012;5:596–9.
[48] Vijayakumar C, Prabhu R, Senthil Velan M, et al. Role of heparin irrigation in the management of superficial burns with special reference to pain relief and wound healing: a pilot study. Cureus 2018;10:e3157.
[49] Jansen PG, Velthuis H, Huybregts RA, et al. Reduced complement activation and improved postoperative performance after cardiopulmonary bypass with heparin-coated circuits. J Thorac Cardiovasc Surg 1995;110:829–34.
[50] Koster A, Sänger S, Hansen R, et al. Prevalence and persistence of heparin/platelet factor 4 antibodies in patients with heparin coated and noncoated ventricular assist devices. ASAIO J 2000;46(3):319–22.
[51] Seffer MT, Cottam D, Forni LG, et al. Heparin 2.0: a new approach to the infection crisis. Blood Purif 2020 Jul:1–7. doi: 10.1159/000508647.
[52] Mycroft-West CJ, Devlin AJ, Cooper LC, et al. Inhibition of BACE1, the β-secretase implicated in Alzheimer's disease, by a chondroitin sulfate extract from Sardina pilchardus. Neural Regen Res 2020;15:1546–53.
[53] Cassinelli G, Torri G, Naggi A. Non-anticoagulant heparins as heparanase inhibitors. Adv Exp Med Biol 2020;1221:493–522.
[54] Kovacsovics TJ, Mims A, Salama ME, et al. Combination of the low anticoagulant heparin CX-01 with chemotherapy for the treatment of acute myeloid leukemia. Blood Adv 2018;2:381–9.
[55] Galli M, Chatterjee M, Grasso M, et al. Phase I study of the heparanase inhibitor roneparstat: an innovative approach for ultiple myeloma therapy. Haematologica 2018;103:e469–72.