1164-1173.
[11] CAI L Z, FOSTER D, KETHMAN W C, et al. Surgical site infections after inguinal hernia repairs performed in low and middle human development index countries: A systematic review[J]. Surg Infect (Larchmt), 2018, 19(1):11-20.
[12] 张明芬, 张学春.腹股沟疝无张力修补术切口感染风险因素分析[J].中华疝和腹壁外科杂志(电子版), 2020, 14(2): 192-194.
[13] BERREVOET F, VANLANDER A, SAINZ-BARRIGA M, et al. Infected large pore meshes may be salvaged by topical negative pressure therapy[J]. Hernia, 2013, 17(1):67-73.
[14] AGNETA M, FRIEDRICH K, FERDINAND K. Evidence for replacement of an infected synthetic by a biological mesh in abdominal wall hernia repair[J]. Front Surg, 2016, 2:67.
[15] WANG D, FU Y, LIU Q, et al. Maximal infected mesh removal with methylene blue injection for mesh infection after inguinal hernia repair[J]. Surg Infect (Larchmt), 2021, 22 (3):347-352.
[16] SILVA A N S, KOUROUMPAS E, FEARNHEAD N, et al. Adhesional small bowel obstruction related to stapling device from previous laparoscopic inguinal hernia repair[J]. BMJ Case Rep, 2019, 12(4):e229377.
[17] YAMAMOTO S, KUBOTA T, ABE T. A rare case of mechanical bowel obstruction caused by mesh plug migration [J]. Hernia, 2015, 19(6):983-985.
[18] GAVRIILIDIS P, DAVIES R J, WHEELER J, et al. Total extraperitoneal endoscopic hernioplasty (TEP) versus Lichtenstein hernioplasty: A systematic review by updated traditional and cumulative meta-analysis of randomised-controlled trials[J]. Hernia, 2019, 23(6):1093-1103.
[19] D'AMORE L, GOSSETTI F, MANTO O, et al. Mesh plug repair: Can we reduce the risk of plug erosion into the sigmoid colon?[J]. Hernia, 2012, 16(4):495-496.
[20] KOLIAKOS N, PAPACONSTANTINOU D, NASTOS C, et al. Intestinal erosions following inguinal hernia repair: A systematic review[EB/OL]. [2021-04-01]. https://doi. org/10.1007/s10029-020-02324-1.
[21] DEMIRAY O, GONULLU D, GEDIK M L, et al. Effects of suture tecnique on mesh shrinkage[J]. Asian J Surg, 2019, 42 (1):224-227.
[22] SCHÄFER M, LAUPER M, KRÄHENBÜHL L. Trocar and Veress needle injuries during laparoscopy[J]. Surg Endosc, 2001, 15(3):275-280.
[23] ANTONIO M, GISELA, JORDI C, et al. Presurgical risk model for chronic postsurgical pain based on 6 clinical predictors: A prospective external validation[J]. Pain, 2020, 161(11):2611-2618.
[24] MELKEMICHEL M, BRINGMAN S, NILSSON H, et al. Patient-reported chronic pain after open inguinal hernia repair with lightweight or heavyweight mesh: A prospective, patient-reported outcomes study[J]. Br J Surg, 2020, 107(12): 1659-1666.
[25] WANG W J, CHEN J Z, FANG Q, et al. Comparison of the effects of laparoscopic hernia repair and Lichtenstein tension-free hernia repair[J]. J Laparoendosc Adv Surg Tech A, 2013, 23(4):301-305.
[26] LEE L D, STROUX A, NICKISCH D, et al. Operative outcome of hernia repair with synthetic mesh in immunocompromised patients[J]. ANZ J Surg, 2020, 90(11):2248-2253.
[27] PROCHOTSKY A, DOLAK S, MINAROVJECH V, et al. Giant inguinoscrotal hernia repair[J].Bratisl Lek Listy, 2017, 118(8):472-478.
[28] SACHIN M, LIN S S. The learning curve for laparoscopic inguinal hernia repair: A newly qualified surgeon perspective [J]. J Surg Res, 2016, 205(1):246-251.

癌症治疗手段相关的栓塞风险

钟伟宁[1],伍 俊[2*] (1.广东医科大学,广东湛江 524000; 2.广东医科大学附属医院呼吸与危重症医学科,广东湛江 524000)

摘 要: 目前有许多针对癌症患者的治疗手段,如手术、化疗、靶向治疗等。近年来,新型分子靶向治疗药物的出现更是取得了满意效果。然而,治疗手段相关风险增加,其中栓塞是重要风险之一。平衡栓塞风险和治疗获益非常重要。了解癌症治疗手段相关栓塞风险,有助于早期识别肺栓塞。该文综述了目前癌症治疗手段及其相关栓塞风险。

关键词: 癌症; 化疗; 靶向治疗; 栓塞
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作者简介: 钟伟宁(1995–),男,在读硕士研究生
通信作者: 伍 俊(1973–),女,博士, E-mail:630206363@qq.com

Risks of cancer therapy-associated embolism

ZHONG Wei-ning[1], WU Jun[2*] (1.Guangdong Medical University, Zhanjiang 524000, China; 2.Department of Respiratory and Critical Care Medicine; Affiliated Hospital of Guangdong Medical University, Zhanjiang 524000, China)

Abstract: There are many cancer treatment, such as surgery, chemotherapy, targeted therapy, and the like. Satisfactory results have been obtained using novel molecular targeted drugs in recent years. However, cancer therapy-associated risks have increased, of which embolization is one of the important risks. It is crucial to balance the embolism risk and treatment benefit. It is helpful in early identification of pulmonary embolism to understand cancer therapy-associated embolism risks. This article reviews current cancer treatment methods and their associated embolism risks.

Key words: cancer; chemotherapy; targeted therapy; embolism

静脉血栓栓塞症（VTE）是恶性肿瘤常见的并发症之一，包括深静脉血栓形成（DVT）和肺血栓栓塞症（PTE）。肺栓塞（PE）形成的栓子类型包括血栓、脂肪栓和空气栓塞等，其中以血栓最为常见，因此通常所称作的肺栓塞即为肺血栓栓塞症。血栓事件的发生常伴随更高的死亡率和不良预后，且因其隐匿性而容易出现漏诊、误诊等，早期的PE诊断和治疗对降低漏诊率、病死率具有重要的意义。本文主要对癌症治疗干预措施相关的血栓风险和其作用机制进行综述，以提高临床对癌症治疗相关VTE的风险预警，权衡治疗和血栓形成的平衡点，改善患者的预后。

1 手术

研究者们针对手术是否作为VTE的危险因素展开了相当多的研究，经历了约半个世纪的时间，手术因素与VTE的关系也逐渐被报道。在国外，一项接受普通泌尿外科手术的研究中，收集了所有泌尿外科手术治疗的病例，目的是为了分析深静脉血栓和肺栓塞的事件，患者在接受手术治疗后30 d内，深静脉血栓事件明显增多，其中主要手术所占的比例为：膀胱切除术/尿流改道术的发生率最高（3.96%），其次为部分膀胱切除术（2.35%）和开放性根治性肾切除术（1.67%）。在同等队列中，对所有手术肺栓塞发生率进行统计后发现，占比最大的是膀胱切除术/尿液转流术（2.85%）[1]。最近，国外一项大型数据研究为了分析得出手术后患者出现VTE的概率，筛选出接受血管手术、胃肠道手术、妇科手术、髋关节或膝盖置换术、骨折等手术的患者，研究后发现，接受所有类型手术治疗后的肺栓塞风险在12周内均显著升高[2]。Daddi等[3]指出，接受胸外科手术治疗后的肺癌患者出现肺栓塞的风险升高，但其形成原因与多种因素有关，相关机制复杂，手术部位的损伤在其中扮演着特定的角色，长的血管残端与原位血栓形成密切相关，原位血栓的脱落可以导致深静脉血栓及肺栓塞事件的发生，除此之外，结扎部位的血管内膜剥离、血管轴的过度倾斜所致的狭窄或血流异常均可能作为潜在的技术因素，从而引起接受手术患者VTE的发生。手术是恶性肿瘤患者中最常见的治疗方法之一，其与VTE的形成密切相关，因此提高对恶性肿瘤患者术后的血栓监测具有十分重要的意义。

2 化疗

Blom等[4]发现，与普通人群相比，接受化学疗法患者的VTE风险增加至少了2倍。一项针对化疗患者出现肺栓塞的研究表明，接受化疗的患者常出现无症状的肺栓塞事件，随之而来的是更高的死亡率与不良预后，无症状肺栓塞因其隐匿性而常被低估[5]。因此临床中更应重视早期预防肺栓塞的发生。

2.1 铂类抗癌药

早在20世纪80年代，便有文献报道了顺铂与血栓形成的关系。一项回顾性研究分析发现，对比恶性肿瘤中选择顺铂与非顺铂的化学疗法，接受顺铂的患者的VTE增加了3倍[6]。以顺铂为基础的化疗相关的广泛血管并发症已得到充分文献证明，在一项前瞻性大数据研究中，铂类药物疗法与VTE显著相关，在此类药物中，接受顺铂治疗的患者与奥沙利铂相比的发生率也更高[7]。

2.2 选择性雌激素受体调节剂（SERM）

他莫昔芬是一种雌激素受体调节剂，在乳腺癌和卵巢癌中应用于抑制癌细胞的生长。有文献发现，他莫昔芬导致静脉血栓栓塞症的风险增加2～7倍[8-10]。他莫昔芬是结构类似雌激素的抗雌激素药物，其通过与雌二醇竞争雌激素受体，与雌激素受体形成稳定复合物，经转运进入癌细胞核内，从而起到抗癌生长的作用。Jiang等[11]提出，他莫昔芬的这种竞争作用，能起到刺激雌激素分泌的水平，从而导致雌激素相关

VTE风险升高的结果。另一种选择性雌激素受体调节剂雷洛昔芬也与血栓的形成有关。一项关于雷洛昔芬在绝经后骨质疏松妇女中引起血栓的研究中，与安慰剂相比，雷洛昔芬的VTE风险增加了2倍[12]。一项纳入多项临床试验的24 523名妇女的荟萃分析显示，雷洛昔芬引起的VTE风险增加了62%[13]。然而，雷洛昔芬的血栓形成风险似乎小于他莫昔芬。在对比雷洛昔芬与他莫昔芬在乳腺癌的一级预防的试验中，雷洛昔芬的VTE风险降低了30%[14]。

2.3　免疫调节药物

免疫调节的亚胺类药物(IMIDs)，诸如沙利度胺和来那度胺等，目前尚未发现单独使用沙利度胺、沙利度胺衍生物或来那度胺会增加VTE的风险。但是，在与糖皮质激素或其他化疗药物联合使用时，会使多发性骨髓瘤(MM)患者发生VTE的风险增加约10%~40%[15]。单独使用沙利度胺时，MM的血栓发生率低于5%，而沙地度胺联合地塞米松治疗的发生率低于10%~20%，沙利度胺化疗的发生率则为20%~40%[16-20]。IMIDs引起VTE的机制是多因素综合影响的。在一项体外细胞实验中发现，沙利度胺具有强化蛋白酶活化受体-1(PAR-1)的表达，血小板和内皮细胞表达的G蛋白偶联受体，能够结合凝血酶并参与血小板的聚集作用，而这种增强作用促进了VTE的形成[21]。在接受沙利度胺治疗的患者中观察到，其内源性抗凝分子蛋白S、抗凝血酶和血栓调节蛋白水平下降，最终引起VTE的发生[22]。也有研究发现，组织因子和血管内皮生长因子的变化，以及活化蛋白C抵抗的作用，可能在血栓形成中起着一定的影响[23-24]。

让人意外的是，在MM患者中，蛋白酶抑制剂硼替佐米似乎能使免疫调节的亚胺类药物引起的血栓作用失效[25]。有研究指出，硼替佐米能引起血小板计数的减少以及抑制血小板的聚集，减少血液黏稠的情况，从而起到抗血栓形成的作用[26]。

3　靶向治疗

3.1　血管内皮生长因子抑制剂(VEGF抑制剂)

对15 956名贝伐珠单抗治疗晚期恶性肿瘤的随机对照试验中的7 956名患者进行荟萃分析的结果显示，服用贝伐珠单抗的患者相对于对照者，发生VTE的RR为1.33[27]。目前，贝伐珠单抗与VTE风险的关系尚未研究清楚，还需要进一步的研究分析。其他新一代的酪氨酸激酶抑制剂(如索拉非尼、舒尼替尼、帕唑帕尼和凡德他尼)，在尚有的meta分析中未发现与血栓形成有关[28-29]。

3.2　表皮生长因子抑制剂(EGFR抑制剂)

有研究发现，西妥昔单抗和帕尼单抗的EGFR抑制剂与VTE的显著增加有关，在对Ⅱ期和Ⅲ期随机对照试验的系统评价中，通过比较有和没有EGFR抑制剂的标准方案，发现VTE的RR为1.5，PE的RR为1.6[30]。

3.3　免疫检查点抑制剂(ICI)

免疫检查点抑制剂是近些年来提出的新型靶向治疗药物，目前主要用于黑色素瘤和非小细胞肺癌等患者的治疗中，ICI的出现无疑给许多癌症患者带来了福音，但其所带来的不良反应需要得到更多的重视。

Sussman等[31]首次提出，免疫检查点抑制剂ICI引发黑色素瘤患者的VTE发生率很高。ICI使用情况下与癌症相关的血栓形成的机制尚未完全明了。多项研究表明，癌细胞是能够通过增加组织因子和纤溶酶原激活因子-1的表达来直接激活凝血级联反应，并释放微粒和激活其他凝血因子[32-35]。另外，癌细胞能够分泌炎性细胞因子，并且刺激宿主细胞产生炎性细胞因子，例如肿瘤坏死因子(TNF)-α和白介素-1β，从而间接地激活了凝血级联反应[36-37]。也有文献报道，通过程序性细胞死亡蛋白1(PD-1)和细胞毒性T淋巴细胞相关蛋白4(CTLA-4)的抑制作用还可以进一步加剧这种已经促炎的状态，炎性细胞因子的产生随后抑制了内皮细胞的抗血栓形成反应并促进了其促凝活性，最终导致静脉血栓的产生[38]。

4　抗代谢药

5-氟尿嘧啶目前应用于多种恶性肿瘤的治疗中，是一种重要的抗代谢类抗癌药物。在最近的一项数据库分析中，研究人员通过随访转移性结直肠癌的患者，确定了5-氟尿嘧啶是11 086例研究病例中VTE的危险因素[39]。5-氟尿嘧啶促进的血栓形成的机制是复杂的。研究表明，5-氟尿嘧啶可以通过诱导血管痉挛从而引起血栓的形成[40]。也有研究发现，5-氟尿嘧啶通过影响自由基的产生(如硝基氧化氮和活性氧)，进而参与血栓形成的过程[41-43]。另外，有研究表明，5-氟尿嘧啶可以引起血管内皮的损伤效应，进而参与血栓的形成[44]。

5　中心静脉导管

中心静脉导管主要用于构建静脉给药的途径、测量中心静脉压和血液透析等，包括中心静脉导管CVC和经外周静脉穿刺中心静脉置管PICC。在癌症

患者中，中心静脉导管被广泛应用以进行化疗。一项研究报道，成人患者中有症状表现的导管相关深静脉血栓形成的发生率为0.3%~28%[45-47]。但很少超过28%的上限值，而通过静脉造影确定的导管相关的深静脉血栓的发生率为30%~60%[48]。中心静脉导管与静脉血栓形成密切相关。最近的一项研究也得出了上述结论，该研究纳入了13例严重感染新型冠状病毒肺炎的患者，目的是为了确定13例患者中心静脉置管后静脉血栓事件的发生率，所有患者因病情需要均进行了体外膜肺氧合，结果发现，所有患者均经历了静脉血栓栓塞：10例（76.9%）发生了与导管相关的深静脉血栓形成，2例（15.4%）发生了独立的肺栓塞，1例（7.7%）发生了与导管相关的深静脉血栓形成和肺栓塞。由此可见，进行体外膜肺氧合治疗患者具有显著的VTE风险[49]。

有研究发现，导管大小、类型、尖端位置、插入部位、导管停留的时间和静脉插入的次数均是导管相关血栓形成的危险因素[50]。目前中心静脉导管引起血栓形成的机制大致如下所述。PICC导管使得手臂周围大部分静脉的横截面直径增加，从而导致静脉的淤积情况[51]。另外，周围插入的中央导管尖端常出现移动，因此容易伤害内皮组织[52]。若再考虑化疗所带来的VTE风险，综合上述病理因素，PICC导管作为血栓形成的理性场所也就理所应当了。在美国进行的一项大规模前瞻性研究发现，血栓形成事件中有70%在插入导管的第1周发生，而在第2周发生了30%，此后再无发现血栓形成[53]。因此，提出2周内预防性抗凝治疗或许具有重要的临床意义。

6 其他治疗

诸如促红细胞生成剂（ESA）和促红细胞生成素（EPO）等常在癌症患者中被用于治疗贫血，特别是血液系统癌症患者。据报道，接受化学放射治疗的阴道癌或宫颈癌患者，使用ESA可使VTE发生率从3%增加到23%[54]。另一项随机对照试验的系统评价中，在3 728例接受ESA治疗的患者中，有229例发生了VTE事件[55]。在对57项试验的评价中发现，接受ESA的癌症患者VTE的RR为1.5~1.67[55-56]。在一项前瞻性研究中，EPO被认为是癌症患者血栓形成的重要因素，OR为1.83[57]。而在另一篇研究报道中，ESA似乎不会增加骨髓增生异常患者深静脉血栓形成的风险[58]。

粒细胞集落刺激因子G-CSF主要用于治疗和预防癌症患者化疗后引起的粒细胞缺乏症，其作用于造血祖细胞，起刺激中性粒细胞系造血细胞的增殖和成熟。在一项前瞻性试验中，在胃肠道癌、肺癌和淋巴瘤的VTE比值比为2.09[57]。接受G-CSF进行干细胞捐赠的健康患者的促凝血因子增加，包括von Willebrand因子、血栓调节蛋白、凝血酶-抗凝血酶复合物、D-二聚体和凝血酶原片段，这可能会影响其中的某些风险，从而导致静脉血栓栓塞的发生[59]。

7 放射疗法

尽管已知辐射会诱发炎症，内皮细胞活化和细胞死亡，但尚未明确是否与血栓形成相关。一项前瞻性研究分析检查DVT的比率后发现，差异无统计学意义，总的VTE复发率也没有统计学意义。同样，辐射也没有被确定为重要的血栓形成危险因素[57]。

8 小结

针对罹患恶性肿瘤的患者，目前已有不少有效的手段用于治疗和改善患者的病情，包括手术、化疗、靶向治疗、放射治疗等。近几年，随着新型化疗药物和靶向治疗药物在恶性肿瘤患者的治疗中大放异彩，相对应的不良事件风险也随之而来。大量研究表明，癌症患者所接受的治疗手段与VTE形成密切有关，因此充分评估癌症患者血栓形成的风险，提高对肺栓塞的预警，平衡癌症患者的治疗干预与风险管理具有十分重要的意义。

参考文献：

[1] TYSONMD, CASTLE E P, HUMPHREYS M R, et al. Venous thromboembolism after urological surgery[J]. J Urol, 2014, 192(3):793-797.

[2] CARON A, N DEPAS, CHAZARD E, et al. Risk of pulmonary embolism more than 6 weeks after surgery among cancer-free middle-aged patients[J]. JAMA Surgery, 2019, 154 (12):1126-1132.

[3] DADDI G, MILILLO G, LUPATTELLI L, et al. Postoperative pulmonary embolism detected with multislice computed tomography in lung surgery for cancer[J]. J Thorac Cardiov Sur, 2006, 132:197-198.

[4] BLOM J W, VANDERSCHOOT J, OOSTINDIER M J, et al. Incidence of venous thrombosis in a large cohort of 66 329 cancer patients:Results of a record linkage study[J]. J Thromb Haemost, 2006, 4(3):529-535.

[5] TISEO M, BERSANELLI M, BARILI M P, et al. Asymptomatic pulmonary embolism in lung cancer:Prevalence and analysis of clinical and radiological characteristics in 141 outpatients[J]. Tumori, 2012, 98(5):594-600.

[6] JIANG D, LEE A I. Thrombotic risk from chemotherapy and other cancer therapies[J]. Cancer Treat Res, 2019, 179:87.

[7] TAN G H C, SHANNON N B, CHIA C S, et al. Platinum agents and mitomycin C-specific complications in cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC)[J]. Int JHyperther, 2018, 34(5):595-600.

[8] DEITCHER S R, GOMES M. The risk of venous thromboembolic disease associated with adjuvant hormone therapy for breast carcinoma[J]. Cancer, 2010, 101(3):439-449.

[9] XU X, CHLEBOWSKI R T, SHI J, et al. Aromatase inhibitor and tamoxifen use and the risk of venous thromboembolism in breast cancer survivors[J]. Breast Cancer Res Treat, 2019, 174(3):785-794.

[10] OPPELT P, BETBADAL A, NAYAK L. Approach to chemotherapy-associated thrombosis[J]. Vasc Med, 2015, 20(2): 153-161.

[11] JIANG D, LEE A I. Thrombotic risk from chemotherapy and other cancer therapies[J]. Cancer Treat Res, 2019, 179:87.

[12] DUVERNOY C S, YEO A A, WONG M, et al. Antiplatelet therapy use and the risk of venous thromboembolic events in the Raloxifene Use for the Heart (RUTH) trial[J]. J Women Health, 2010, 19(8):1459-1465.

[13] ADOMAITYTE J, FAROOQ M, QAYYUM R. Effect of raloxifene therapy on venous thromboembolism in postmenopausal women: A meta-analysis[J]. Thromb Haemost, 2008, 99(2):338-342.

[14] VOGEL V G, COSTANTINO J P, WICKERHAM D L, et al. Effects of tamoxifen vs raloxifene on the risk of developing invasive breast cancer and other disease outcomes: The NSABP Study of Tamoxifen and Raloxifene (STAR) P-2 Trial[J]. JAMA, 2016, 295(23):2727-2741.

[15] JIANG D, LEE A I. Thrombotic risk from chemotherapy and other cancer therapies[J]. Cancer Treat Res, 2019, 179: 87-101.

[16] HADDAD T C, GREENO E W. Chemotherapy-induced thrombosis[J]. Thromb Res, 2006, 118(5):555-568.

[17] OPPELT P, BETBADAL A, NAYAK L. Approach to chemotherapy-associated thrombosis[J]. Vas Med, 2015, 20(2): 153-161.

[18] RAJKUMAR S V. Combination therapy with thalidomide plus dexamethasone for newly diagnosed myeloma[J]. J Clin Oncol, 2002, 20(21):4319-4323.

[19] ZANGARI M. Increased risk of deep-vein thrombosis in patients with multiple myeloma receiving thalidomide and chemotherapy[J]. Blood, 2001, 98(5):1614-1615.

[20] PALUMBO A, RAJKUMAR S V, DIMOPOULOS M A, et al. Prevention of thalidomide-and lenalidomide-associated thrombosis in myeloma[J].Leukemia, 2008, 22(2):414-423.

[21] KAUSHAL V, KAUSHAL G P, MELKAVERI S N, et al. Thalidomide protects endothelial cells from doxorubicin-induced apoptosis but alters cell morphology[J]. J Thromb Haemost, 2004, 2:327-334.

[22] RODEGHIERO F, ELICE F. Thalidomide and thrombosis [J]. Pathophysiol Haemost Thromb, 2003, 33(1):15-18.

[23] PALUMBO A, PALLADINO C. Venous and arterial thrombotic risks with thalidomide:evidence and practical guidance [J]. Ther Adv Drug Saf, 2012, 3(5):255-266.

[24] ZANGARI M, SAGHAFIFAR F, ANAISSIE E, et al. Activated protein C resistance in the absence of factor V Leiden mutation is a common finding in multiple myeloma and is associated with an increased risk of thrombotic complications[J]. Blood Coagul Fibrin, 2002, 13(3):187-192.

[25] ZANGARI M, FINK L, ZHAN F, et al. Low venous thromboembolic risk with bortezomib in multiple myeloma and potential protective effect with thalidomide/lenalidomide-based therapy:review of data from phase 3 trials and studies of novel combination regimens[J]. Clin Lymphoma Myeloma Leuk, 2011, 11(2):228-236.

[26] ZANGARI M, GUERRERO J, CAVALLO F, et al. Hemostatic effects of bortezomib treatment in patients with relapsed or refractory multiple myeloma[J]. Haematologica, 2008, 93(6): 953-954.

[27] NALLURI S R, CHU D, KERESZTES R, et al. Risk of venous thromboembolism with the angiogenesis inhibitor bevacizumab in cancer patients: a meta-analysis[J]. JAMA, 2008, 301(19):2277-2285.

[28] OPPELT P, BETBADAL A, NAYAK L. Approach to chemotherapy-associated thrombosis[J]. Vasc Med, 2015, 20(2): 153-161.

[29] QI W X, MIN D L, SHEN Z, et al. Risk of venous thromboembolic events associated with VEGFR-TKIs: a systematic review and meta-analysis[J]. Int J Cancer, 2013, 132(12): 2967-2974.

[30] MIRODDI M, STERRANTINO C, SIMMONDS M, et al. Systematic review and meta-analysis of the risk of severe and life-threatening thromboembolism in cancer patients receiving anti-EGFR monoclonal antibodies (cetuximab or panitumumab)[J]. Int J Cancer, 2016, 139(10):2370-2380.

[31] SUSSMAN T A, LI H, HOBBS B, et al. Incidence of thromboembolism in patients with melanoma on immune checkpoint inhibitor therapy and its adverse association with survival[J]. J Immuno Ther Cancer, 2021, 9(1):e001719.

[32] KHORANA A A, AHRENDT S A, RYAN C K, et al. Tissue factor expression, angiogenesis, and thrombosis in pancreatic cancer[J]. Clin Cancer Res, 2007, 13(10):2870-2875.

[33] DEEPAK V, RAMACHANDRAN S, BALAHMAR R M, et al. In vitro evaluation of anticancer properties of exopolysaccharides from Lactobacillus acidophilus in colon cancer

cell lines[J]. Vitro Cell Dev Biol Anim, 2016, 52(2):163-173.

[34] LUPU-MEIRI M, GERAS-RAAKA E, LUPU R, et al.Knockdown of plasminogen-activator inhibitor-1 enhances expression of E-cadherin and promotes epithelial differentiation of human pancreatic adenocarcinoma cells[J]. J Cell Physiol, 2012, 227(11):3621-3628.

[35] MUHSIN-SHARAFALDINE M R, SAUNDERSON S C, DUNN A C, et al. Procoagulant and immunogenic properties of melanoma exosomes,microvesicles and apoptotic vesicles [J]. Oncotarget, 2016, 7(35):56279-56294.

[36] PONS S, FSDIL S, AZOULAY E, et al. The vascular endothelium: The cornerstone of organ dysfunction in severe SARS-CoV-2 infection[J]. Crit Care, 2020, 24(1):353.

[37] FALANGA A, PANOVA-NOEVA M, RUSSO L. Procoagulant mechanisms in tumour cells[J]. Best Pract Res Clin Haematol, 2009, 22(1):49-60.

[38] SATO R, IMAMURA K, SAKATA S, et al. Disorder of coagulation-fibrinolysis system: An emerging toxicity of Anti-PD-1/PD-L1 monoclonal antibodies[J]. J Clin Med, 2019, 8(6):762.

[39] PULLURI B, LITTENBERG B, LAL I, et al. Risk factors for venous thromboembolism in metastatic colon cancer patients in the contemporary treatment era: A seer-medicare data analysis[J]. Blood, 2016, 128(22):2598-2598.

[40] MORIYAMA S, YOKOYAMA T, IRIE K, et al. Atrial fibrillation observed in a patient with esophageal cancer treated with fluorouracil[J]. J Cardiol Cases, 2019, 20(5):183-186.

[41] KINHULT S, ALBERTSSON M, ESKILSSON J, et al. Effects of probucol on endothelial damage by 5-fluorouracil [J]. Acta Oncol, 2003, 42:304-308.

[42] MAVRIKOU S, TSEKOURAS V, KARAGEORGOU M A, et al. Detection of superoxide alterations induced by 5-fluorouracil on HeLa cells with a cell-based biosensor[J].Biosensors, 2019, 9(4):126.

[43] FOCACCETTI C, BRUNO A, MAGNANI E, et al. Effects of 5-fluorouracil on morphology, cell cycle, proliferation, apoptosis, autophagy and ros production in endothelial cells and cardiomyocytes[J]. Plos One, 2015, 10(2):e0115686.

[44] POLK A, VISTISEN K, VAAGENILSEN M, et al. A systematic review of the pathophysiology of 5-fluorouracil-induced cardiotoxicity[J]. BMC Pharmacol Toxicolv, 2014, 15(1):47.

[45] AW A, CARRIER M, KOCZERGINSKI J, et al. Incidence and predictive factors of symptomatic thrombosis related to peripherally inserted central catheters in chemotherapy patients[J]. Thromb Res, 2012, 130(3):323-326.

[46] VERSO M, AGNELLI G. Venous thromboembolism associated with long-term use of central venous catheters in cancer patients[J]. J Clin Oncol, 2003, 21(19):3665-3675.

[47] KING M M, RASNAKE M S, RODRIGUEZ R G, et al. Peripherally inserted central venous catheter-associated thrombosis: retrospective analysis of clinical risk factors in adult patients[J]. South Medl J, 2006, 99(10):1073-1077.

[48] DEBOURDEAU P, ZAMMIT C, PAVIC M, et al. Venous thromboembolism associated with long-term use of central venous catheters in cancer patients[J]. La Revue de Médecine Interne, 2007, 28(7):471-483.

[49] PARZY G, DAVIET F, PUECH B, et al. Venous thromboembolism events following venovenous extracorporeal membrane oxygenation for severe acute respiratory syndrome coronavirus 2 based on CT scans[J]. Critl Care Med, 2020, 48(10):e971-e975.

[50] GALLIENI M, PITTIRUTI M, BIFFI R. Vascular access in oncology patients[J]. CA Cancer J Clin, 2010, 58(6):323-346.

[51] NIFONG T P, MCDEVITT T J. The effect of catheter to vein ratio on blood flow rates in a simulated model of peripherally inserted central venous catheters[J]. Chest, 2011, 140(1):48-53.

[52] SONG L, LI X, GUO Y, et al. Malposition of peripherally inserted central catheter: experience from 3012 cancer patients[J]. Int J Nurs Pract, 2014, 20(4):446-449.

[53] WALSHEL J. Complication rates among cancer patients with peripherally inserted central catheters[J]. J Clin Oncol, 2002, 20(15):3276-3281.

[54] HADDAD T C, GREENO E W. Chemotherapy-induced thrombosis[J]. Thromb Res, 2006, 118(5):555-568.

[55] BOHLIUS J, WILSON J, SEIDENFELD J, et al. Erythropoietin or darbepoetin for patients with cancer[J]. Cochrane Database Syst Rev, 2009, 3(3):CD007303.

[56] TONIA T, METTLER A, ROBERT N, et al. Erythropoietin or darbepoetin for patients with cancer[J]. Cochrane Database Syst Revs, 2012, 12(12):CD003407.

[57] KHORANA A A, FRANCIS C W, CULAKOVA E, et al. Risk factors for chemotherapy-associated venous thromboembolism in a prospective observational study[J]. Cancer, 2010, 104(12):2822-2829.

[58] SMITH S W, SATO M, GORE S D, et al. Erythropoiesis-stimulating agents are not associated with increased risk of thrombosis in patients with myelodysplastic syndromes[J]. Haematologica, 2012, 97(1):15-20.

[59] OPPELT P, BETBADAL A, NAYAK L. Approach to chemotherapy-associated thrombosis[J]. Vas Med, 2015, 20(2):153-161.