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胸腔灌注抗血管生成药物治疗恶性胸腔积液的研究进展

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摘　要

恶性胸腔积液(malignant pleural effusion, MPE)是晚期癌症的常见及严重并发症，可不同程度地引起胸闷、胸痛、呼吸困难等不适症状，这对于晚期癌症患者无疑是雪上加霜。此外，恶性胸腔积液的存在会降低患者的整体表现状态，从而影响他们接受可能延长生命的抗癌治疗的可能性。以往，多以反复胸腔内置管引流为恶性胸腔积液的主要治疗手段，但单纯的胸腔内置管引流一方面无法解决胸腔积液反复产生的问题；另一方面因多次进行胸腔穿刺将不可避免地导致胸腔内感染、组织纤维化等并发症。目前，针对恶性胸腔积液的主要治疗方法是，对原发恶性肿瘤进行全面系统的全身化疗，同时针对胸腔积液做局部治疗，其中，胸腔内药物灌注治疗正进一步成为控制恶性胸腔积液产生的主要手段。经国内外多项研究证明，铂类药物、贝伐珠单抗、重组人血管内皮抑素等药物对恶性胸腔积液的产生有抑制作用。本文讨论两种抗血管生成药物(贝伐珠单抗、重组人血管内皮抑素)胸腔内灌注治疗(intrapleural perfusion therapy, IPT)恶性胸腔积液的疗效及其安全性。旨在为恶性胸腔积液治疗提供些许思路。

关键词

恶性胸腔积液，胸腔内灌注治疗，抗血管生成药，贝伐珠单抗，重组人血管内皮抑素

Research Progress in the Treatment of Malignant Pleural Effusion with Intrathoracic Perfusion of Antiangiogenic Drugs

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Abstract

Malignant pleural effusion (MPE) is a common and serious complication of advanced cancer, which can cause chest tightness, chest pain, dyspnea and other discomfort symptoms to varying degrees, which is undoubtedly worse for patients with advanced cancer. In addition, the presence of malignant pleural effusion will reduce the overall performance of patients, thus affecting their possibility of receiving anti-cancer treatment that may prolong life. In the past, the main treatment method for malignant pleural effusion was to drain the pleural effusion repeatedly, but on the one hand, the simple drainage of pleural effusion could not solve the problem of repeated pleural effusion; On the other hand, multiple thoracentesis will inevitably lead to complications such as intrathoracic infection and tissue fibrosis. At present, the main treatment methods for malignant pleural effusion are comprehensive and systematic systemic chemotherapy for primary malignant tumors, and local treatment for pleural effusion. Among them, intrathoracic drug infusion therapy is further becoming the main means to control the production of malignant pleural effusion. Many studies at home and abroad have proved that platinum drugs, bevacizumab, recombinant human endostatin and other drugs can inhibit the production of malignant pleural effusion. This article discusses the efficacy and safety of two anti angiogenic drugs (bevacizumab and recombinant human endostatin) in the treatment of malignant pleural effusion (IPT). It aims to provide some ideas for the treatment of malignant pleural effusion.

Keywords

Malignant Pleural Effusion, Intrathoracic Perfusion Therapy, Anti Angiogenic Agents, Bevacizumab, Recombinant Human Endostatin

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1. 引言

恶性胸腔积液(malignant pleural effusion, MPE)是由非小细胞型肺恶性肿瘤、淋巴瘤、乳腺恶性肿瘤及结肠恶性肿瘤等恶性肿瘤进展至晚期发生胸膜转移引起或由恶性胸膜间皮瘤引起。由恶性肿瘤细胞转移至壁层及脏层胸膜之间，损伤胸膜血管内皮细胞并阻塞淋巴管致使淋巴液回流障碍、血液中的液体不断地渗出，不断积聚形成胸腔积液[1] [2]。晚期恶性肿瘤患者一旦产生胸腔积液，随着胸腔积液的不断增加将逐渐影响患者的循环及呼吸功能，患者的生活质量将进一步下降，且提示大多数胸腔积液患者总体预后不佳，中位生存期为3~12个月[3]。随着研究发现，血管内皮生长因子(vascular endothelial growth factor, VEGF)是恶性胸腔积液产生过程中最关键的因子之一，血管内皮生长因子通过激活血管内皮生长因子受体-2 (vascular endothelial growth factor receptor, VEGFR-2)来参与到浆膜腔积液形成中[4]。通过与内源性血管内皮生长因子竞争性结合其受体，抗血管生成药物发挥着抑制新生血管生成的作用，同时又能通过降低血管通透性，达到有效抑制恶性胸腔积液的发生发展，从而延缓肿瘤发展进程。近些年，越来越多的国内外研究来具体探讨贝伐珠单抗、重组人血管内皮抑素两种抗血管生成药物用于胸腔灌注治疗恶性胸腔积液的实际疗效及其安全性，现本文将对此两种抗血管生成药物胸腔灌注治疗恶性胸腔积液在临床上的应用现状及未来发展方向作一篇综述。

2. VEGF 在恶性胸腔积液发病机制中的作用

早在 1971 年，Folkman 就认识到肿瘤微环境的作用，并提出肿瘤的生存生长离不开血管不断地供应，抗血管生成疗法将在癌症治疗中发挥着举足轻重的作用[5]。随着不断深入研究，使我们对 VEGF 在恶性肿瘤中的作用机制有了更进一步的了解，VEGF 是肿瘤血管生成最重要的调节因子之一这一说法已被多数人所公认[6] [7]。

VEGF 是包括 VEGFA、B、C、D、E 和胎盘生长因子的一个内皮生长因子家族这一家族在胸腹腔积液、癌症、缺氧损伤和正常生长发育中都承担着强大的角色[8]。随着研究的进一步深入，更多的研究表明 VEGF 的过度表达与多种恶性肿瘤的发生发展过程有着严密的联系。据报道，多种类型恶性肿瘤患者的血清中以及其引起的胸腔积液中 VEGF 的水平显著升高[9]，特别是在消化系统肿瘤中，更是扮演着不可替代的角色，包括胰腺恶性肿瘤[10] [11]、胃恶性肿瘤[12] [13]和结肠恶性肿瘤[14] [15]等肿瘤中，更是与这些肿瘤的不良预后存在着强烈的联系。尤其是 VEGF 在恶性胸腔积液发生过程中的作用成为广泛研究的焦点，越来越多的证据强烈表明其在胸腔积液发生过程中的中心作用[16]以及其作为治疗靶点的潜力[17] [18]。VEGF 可特异性结合三种 VEGFR (VEGFR1、-2 和-3)中的一种或多种类型激活，VEGFR 通过自身磷酸化，随后激活磷酸肌醇磷脂酶 C、一氧化氮合酶、丝裂原活化蛋白激酶(mitogen activated protein kinase, MAPK)、磷酸肌醇 3-激酶及转录激活剂(transcriptional activator STAT) 3 和 STAT5 等细胞类型依赖性信号级联[19]。VEGF-VEGFR 相互作用后还可以逐步激活下游的 MAPK1 信号级联，以调节内皮细胞增殖和迁移，从而对血管内皮细胞产生多种影响，包括存活、增殖、分化、发芽和形成[20] [21]。这也奠基了其在血管生成中的关键地位，VEGF 不仅在血管舒张中发挥强大作用[22]，还能发挥提高血管[23]和间皮通透性[24]的作用。胸腔内肿瘤细胞产生的 VEGF 参与了胸腔积液形成、肿瘤细胞扩散、血管生成等步骤被多项研究所证明[25] [26]，VEGF 是一种诊断和治疗恶性胸腔积液有前途的研究方向。

3. 贝伐珠单抗在恶性胸腔积液治疗中的运用

贝伐珠单抗(Avastin, Roche)作为首个血管内皮生长因子 A (VEGFA)人源化单克隆抗体，在减弱 VEGFA 依赖性肿瘤血管形成方面起着关键作用，因此被广泛用于肺恶性肿瘤、妇科肿瘤及其恶性积液的治疗中[27]。贝伐珠单抗与 VEGFA 结合从而抑制血管内皮细胞的增殖、迁移和分化，促进内皮细胞凋亡，使肿瘤血管正常化及肿瘤细胞凋亡，抑制 VEGF 诱导的新生血管生成和血管通透性，最终达到缩小肿瘤的目的[28]。目前关于贝伐珠单抗的最佳用途尚未形成统一标准，但其理论上，与静脉输注相比，胸腔内灌注具有一些优势，包括治疗剂的局部特定浓度和较低的总剂量。此外，胸膜腔的封闭性使其成为胸腔给药的理想场所。Nie [29]等人进行了一项共计纳入 43 名非小细胞肺癌(Non-small cell lung cancer, NSCLC)伴胸腔积液患者的研究，来比较分析贝伐珠单抗在胸腔内灌注或静脉内注射的疗效对比，发现胸腔内灌注组在缓解率、有效率、血清 VEGF 水平中值降低幅度优于静脉注射组。且有关于贝伐珠单抗的不良反应如高血压、蛋白尿和鼻出血，本研究中静脉注射组比胸腔内灌注组发生率更高，本研究最终得出贝伐珠单抗胸腔内灌注在治疗 NSCLC 引起的恶性胸腔积液方面具有更高的效率和更高的安全性这一结论。这也坚定了我们对贝伐珠单抗未来胸腔灌注治疗恶性胸腔积液的强大信念。另外，有研究证明贝伐珠单抗与多种化疗药物协同作用[30] [31]，使其成为恶性胸腔积液临床治疗的潜在候选药物。一篇关于贝伐珠单抗联合化疗治疗非小细胞肺癌伴恶性胸腔积液的回顾性综述中[32]，13 名患者中有 12 名患者的恶性胸腔积液控制时间超过 8 周，无积液再累积的中位无进展生存时间为 312 天。近期，一项关于贝伐珠单抗治疗伴有恶性胸腔积液的非鳞状非小细胞肺癌患者前瞻性随机对照 II 期临床研究[33]，针对 20 名患有恶性胸腔积液的非鳞状非小细胞肺癌患者进行单剂贝伐珠单抗胸膜腔内注射。恶性胸腔积液的客观有效率为 50%。恶性胸腔积液的中位 PFS 为 7.0 个月，也说明贝伐珠单抗单药对恶性胸腔积液非鳞状 NSCLC

患者有一定疗效。上述研究均表明，胸腔内注射贝伐珠单抗能有效控制恶性胸腔积液，缓解呼吸困难、发绀等症状，提高患者生活质量，延长生存期。这些研究进一步证明了恶性胸腔积液靶向抗血管生成疗法的临床价值。

4. 重组人血管内皮抑素(Endostatin, Endostar)在恶性胸腔积液治疗中的运用

重组人血管内皮抑素(endostatin)是一种新型内源性血管生成抑制剂，具有抗肿瘤活性。血管内皮抑素是一种天然存在于 18 型胶原的 20 kDa C 末端片段，由正常细胞和组织释放，血管内皮抑素能够特异性抑制内皮细胞的增殖，并能有效抑制血管的生成及生长[34] [35]。据报道，内皮抑素可以抑制多种肿瘤的血管生成，其中包括肺癌、胃癌[36]和结肠癌[37] [38] [39] [40]并可能干扰生长因子的促血管生成作用。毛细血管内皮细胞是内皮抑制素的靶点，内皮抑制素阻断内皮细胞增殖和新血管的形成，并影响恶性肿瘤的进展和转移[35]。Endostatin 已通过腔内注射用于治疗恶性浆液性积液，包括恶性胸腔积液和恶性腹腔积液。证据表明，单独或联合化疗药物治疗癌症患者恶性浆液性积液是安全有效的[41] [42] [43]。Ma [44]等人进行了一项动物研究，将表达增强型绿色荧光蛋白的 Lewis 肺癌细胞系注入胸膜腔内，建立 MPE 小鼠模型，分别向胸膜腔内注射高剂量 Endostatin (30 mg/kg)、低剂量 Endostatin (8 mg/kg)、生理盐水或贝伐单抗(5 mg/kg)，结果表明高剂量 Endostatin 治疗组的胸腔积液体积、胸腔肿瘤灶数量和 VEGF-A 表达比其他组别显著减少。一些研究已经表明，抗血管生成药物治疗肿瘤除了能降解现有的肿瘤血管和抑制肿瘤血管生成外，还可以通过降低肿瘤内的压力和使肿瘤血管正常化来促进细胞毒性药物的渗透和分布，在 MPE 治疗中发挥了有效的抗癌作用，为 Endostatin 治疗 MPE 提供了一定的理论依据[45]。Rong [46]等人进行了一项关于 Endostatin 联合化疗药物与单独化疗药物胸腔灌注治疗恶性胸腔积液的系统评价和荟萃分析，经过分析总结了 13 项随机对照试验，发现 Endostatin 通过胸腔灌注与化疗药物联合治疗 MPE 的 ORR (overall response rate)和 DCR (disease control rate)效益优于单独化疗药物(优势比分别为 3.58；2.97)。关于重组人血管内皮抑素的剂量应用问题，国内进行了一系列研究，林等人[47]进行了一项关于不同剂量重组人血管内皮抑素胸腔灌注对 IV 期肺腺癌伴胸腔积液的临床疗效的回顾性研究，共纳入 140 例患者，对照组给予胸腔注入重组人血管内皮抑素 45 mg；观察组给予胸腔注入重组人血管内皮抑素 90 mg，最终发现观察组临床症状缓解率(51.43%)高于对照组(34.29%, $P < 0.05$)，观察组日常生活改善能力(84.29%)高于对照组(74.29%, $P < 0.05$)。杨等人[48]收集了 92 例恶性胸腔积液患者来研讨不同剂量恩度(Endostatin)胸腔灌注治疗恶性胸腔积液的总有效率及安全性的比较。结果胸腔注入恩度 30 mg 总有效率为 65.5%、60 mg 的总有效率为 75.0%、90 mg 的总有效率为 83.9%，表明肺癌恶性胸腔积液患者胸腔灌注不同浓度的恩度整体疗效都较好，可有效减少恶性胸腔积液生成、改善患者生活质量、提升临床疗效，值得进一步推广。这些结果证实了 Endostatin 的胸腔灌注在控制 MPE 中发挥了积极作用，这表明它是治疗 MPE 的一种新的潜在治疗选择，是控制 MPE 的安全的、有效的药物，值得我们进一步研究探索。

5. 小结与展望

过去数十载，由于各种治疗和相关临床研究的百花齐放、百家争鸣，人类在癌症的治疗方面不断取得进步，进一步改善了当前恶性肿瘤患者的困境，使得人们愈发坚定信念寻找方法来治疗而不仅仅是缓解胸腔积液的症状。由于血管生成在胸腔积液中起着关键作用，因此恶性胸腔积液治疗的注意力不可避免地集中在抗血管生成治疗上，特别是贝伐珠单抗、重组人血管内皮抑素这两种抗血管生成药物。Endostatin 和贝伐珠单抗在临床应用中获批后，全球范围内进行了大量的临床研究。这些研究表明 Endostatin 和贝伐珠单抗治疗 MPE 是安全有效的，尤其在治疗 NSCLC 方面提供了强有力的证据。经过系统的治疗，NSCLC 和 MPE 患者生活质量大大提高，随之而来的是生存率的不断提高。然而，迄今为

止，暂未有大型前瞻性 III 期研究探究抗血管生成药物对恶性胸腔积液的益处，这是一个值得我们更多关注及探索的问题。此外，上述文中的大多数研究，无论是前瞻性的还是回顾性的，大多是由中国或日本团体进行的，这不可避免的导致研究结果的地理和种族差异。所以，我们仍迫切需要其他族裔群体提供更多有效数据，我们也时刻期盼这些正在进行或即将进行的临床研究能给恶性肿瘤患者带来新的希望。总之，未来抗血管生成药物用于治疗恶性胸腔积液的进一步调查研究仍任重而道远，如何提高恶性胸腔积液患者的治疗效果和生活质量是未来的研究方向。无论何时，面对疾病我们均应以坚实、科学的理论为基础，以临床实际需求为指导，谨慎前行。

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