Medical Diagnosis 医学诊断, 2011, 1, 1-5
http://dx.doi.org/10.12677/md.2011.11001 Published Online September 2011 (http://www.hanspub.org/journal/md/)

Bevacizumab: Current Approach in the Treatment of Hepatocellular Carcinoma

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Received: Sep. 1st, 2011; revised: Sep. 16th, 2011; accepted: Sep. 21st, 2011.

Abstract: With the continuous development of biotherapy, anti-angiogenesis drug-bevacizumab has become clinical molecular targeted therapy for live cancer, a first-line treatment for patients with advanced hepatocellular carcinoma. Bevacizumab (Avastin; Genentech Inc, South San Francisco, CA), a recombinant humanized monoclonal antibody that targets VEGF, it's efficiently combination of VEGF can prevent VEGF combined with tumor vascular endothelial cell surface receptors (Flt-1 and KDR), thus inhibits cell proliferation and angiogenesis of the tumor. Hepatocellular carcinoma (HCC) is a vascular tumor with poor prognosis, and closely related to angiogenesis. Currently, numerous of studies confirmed the efficacy and tolerability of bevacizumab in HCC. This review attempts to summarize the progress of bevacizumab in HCC and raises new possibilities of interventional therapy in the treatment of hepatocellular carcinoma with the help of Bevacizumab.

Keywords: Bevacizumab; Hepatocellular Carcinoma; Biotherapy; Interventional Therapy

贝伐单抗在肝癌治疗中的应用现状及进展

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收稿日期：2011 年 9 月 1 日；修回日期：2011 年 9 月 16 日；录用日期：2011 年 9 月 21 日

摘　要：随着肝癌生物疗法的不断发展，抗血管生成药－贝伐单抗已用于临床中晚期肝癌的分子靶向性治疗。贝伐单抗作为一种人工合成针对血管内皮生长因子(vascular endothelial growth factor ,VEGF)重组人源化单克隆 IgG1 抗体，可高效结合 VEGF 并防止其与肿瘤血管内皮细胞表面的受体(Flt-1 和 KDR)结合，进而精准抑制肿瘤血管内皮细胞增殖和肿瘤血管的新生。肝癌是一种预后较差的富血管性肿瘤，新生血管的形成与肝癌的发生发展有着密切的关系。大量临床实验(包括人体、动物和细胞水平实验)已经证实贝伐单抗及联合其他疗法靶向性治疗肝癌的有效性。本文将贝伐单抗用于肝癌治疗的应用现状及用于综合性介入治疗肝癌的可行性进行综述。

关键词：贝伐单抗；肝癌；生物疗法；介入治疗

1. 引言

原发性肝细胞癌(hepatocellular carcinoma，HCC)是世界上常见的恶性肿瘤之一，其每年患病者已逾一百万人，因其生长浸润速度快，并常合并有肝硬化，所以就诊患者多数为中晚期肝癌。目前，临床上原位肝移植、手术切除和局部破坏治疗(注射酒精或醋酸，热消融等)等外科治疗手段存在着供体匮乏、术后并发症多、肿瘤易复发与转移，以及部分晚期肝癌患者无法或者不能耐受手术等诸多弊端。经肝动脉局部注射抗癌药物和栓塞肿瘤血管被公认为目前介入治疗晚期

肝癌的首选方法，但术后肿瘤的转移和复发始终影响着介入治疗的疗效和患者的远期生存率[1]。近年来随着肿瘤细胞生物学和分子生物学的发展，生物疗法也逐渐兴起，提高肝癌总体疗效的综合治疗方法成为研究热点。

贝伐单抗(阿瓦斯汀)是一种重组人源化单克隆抗体，于 2004 年 2 月首次获美国食品药品管理局(FDA)批准上市。作为第一种 FDA 批准上市的抗血管生成药物，贝伐单抗可高效结合血管内皮生长因子(VEGF)并防止其与内皮细胞表面的受体(Flt-1 和 KDR)结合，从而阻断和拮抗血管内皮生长因子的生理功能[2,3]。对贝伐单抗的抗血管生成作用研究以及其应用于综合治疗肝癌研究也已经成为一个热点。

2. 血管生成与肝癌

新生血管形成，在肿瘤发生发展中扮演着重要角色，血管新生不仅是肿瘤形成的先决条件，也是肿瘤浸润和转移的重要因素[4]。Fernandez 等[5]研究发现，肝脏血管构架的破坏与新生血管的形成可增加肝血管阻力，降低肝脏血流灌注，进而导致门脉高压，促进进展期肝硬化和肝癌的形成。在侵袭性或转移性肝癌(HCC)患者肿瘤细胞中也发现了血管内皮因子(VEGF)的高表达，Li[6]等同时发现血管内皮生长因子(VEGF)mRNA 在 HCC 中的高表达，在肿瘤进展相关性血管生成以及肝癌的侵袭和转移中发挥了重要的作用。虽然正常肝脏中也存在 VEGF 较低且稳定的表达，但肝癌作为一种富血管肿瘤，VEGF 在肝癌组织中的表达显著高于癌旁组织，研究发现 VEGF 的高表达与肿瘤大小、恶性程度以及转移灶多少都有相关性[7,8]。肝癌组织中 VEGF 的高表达甚至可以用作肝癌术后复发与转移的独立预测指标，并且具有评估肝癌预后的临床应用价值[9]。

3. VEGF 概述

血管内皮生长因子(VEGF)是 1983 年由美国的 Senger 等[10]首先发现，并由 Ferrara 等[11]从体外培养的牛垂体星状细胞中分离出的一种糖蛋白，其由两个相同的多肽链通过二硫键交联而成。VEGF 作为一个细胞因子家族，包括有 VEGF-A、VEGF-B、VEGF-C、VEGF-D、VEGF-E 和胎盘生长因子(Placental growth factor，PLGF)等多个成员，他们都有相似的核苷酸序列，并且都与同一类酪氨酸激酶受体结合[12]。

目前已知 VEGF 受体(vascular endothelial growth factor，VEGFR)有三种：VEGFR-1(Flt-a)、VEGFR-2(Flk-1/KDR)和 VEGFR-3(Flt-4)，且都是特异性存在于内皮细胞的酪氨酸激酶受体[12]。

VEGF 表达的调节受到诸多因素的影响，其中组织乏氧是调控包括缺氧诱导因子-1(hypoxia inducible factor 1，HIF-1)和 VEGF 转录表达的关键因素[13]。细胞因子、激素及原癌基因和抑癌基因表达产物也对 VEGF 的表达产生一定的影响[14-18]。

原位杂交研究已经证明 VEGF mRNA 在人类多种肿瘤组织中表达[19]，肺癌[20]、乳腺癌[21]、胃肠道肿瘤[22]、肾脏肿瘤[23]、卵巢癌[24]和肝癌[25]。实验室研究发现，针对多种肿瘤的 VEGF 单克隆抗体会对其相应肿瘤细胞株的生长产生强有力的抑制作用[26-29]。

鼠抗人血管内皮生长因子单克隆抗体 A.4.6.1 (murine anti-VEGF Mab A.4.6.1)作为贝伐单抗(阿瓦斯汀)的前体，具有很强的抗肿瘤血管生成活性，Kim 等[30]通过建立人类肿瘤裸鼠模型研究发现 70%以上肿瘤血管密度降低，肿瘤生长受到抑制。Warren 等[31]研究该抗体拮抗 VEGF 作用，对鼠大肠癌原发瘤和转移瘤均有抑制作用。Presta 等[32]研究鼠抗人 VEGF 单克隆抗体 A.4.6.1 (muMAb VEGF)和人源化 VEGF 单克隆抗体 A.4.6.1 (rhuMAb VEGF)体外对牛肾上腺新生毛细血管内皮细胞生长影响时发现，二者均可有效的抑制牛牛毛细血管内皮细胞的增殖，且药效和功效相当；同时在对移植有人类 A673 横纹肌肉瘤细胞的雌性 BALB/c 裸鼠治疗的体内实验中发现，muMAb VEGF A.4.6.1 与 rhuMAb VEGF A.4.6.1 均能有效的抑制肿瘤的增长，且后者抑制作用较强。

4. 贝伐单抗在抗肝癌血管生长中应用和进展

贝伐单抗自批准上市以来便与 5-氟尿嘧啶联合应用，用于晚期结直肠癌的一线化疗用药。贝伐单抗与其他药物联合应用可以使肿瘤局部血管瞬时正常化，从而增加化疗药物和氧气向肿瘤部位输送，同时贝伐单抗又能抑制化疗药诱发产生局部缺氧所诱发 VEGF 表达的作用，如果合理计划使用抗血管生成药物与化

学药物，可以增加传统化疗方法的疗效[33]。目前，贝伐单抗联合吉西他滨和奥沙利铂用于晚期肝癌的治疗已经成为研究热点，在第二阶段的临床试验中，Zhu等[34]发现，在不同治疗周期中吉西他滨与奥沙利铂联合应用抗血管生成药物－贝伐单抗，可以一定程度的延长晚期肝癌患者的远期生存率(PFS)。Lassau[35]等在最新的研究中也证实了贝伐单抗可显著减少肿瘤区域的血流灌注。在评价贝伐单抗应用于不可切除肝癌的临床和生物学效应时，Siegel 等[36]等发现，贝伐单抗可以提高远期生存率(PFS)40%~60%，同时其对患者血浆中的细胞因子水平也有影响。随后对贝伐单抗联合卡培他滨作为晚期肝癌一线治疗的疗效和耐受性研究中，发现该组合具有良好的耐受性和抗肿瘤活性[37]。Ong 等[38]在对小鼠移植性肝癌实验中应用贝伐单抗联合雷帕霉素的研究中，应用 PET-CT 生物成像对小鼠肝癌的进展进行评估发现应用贝伐单抗联合雷帕霉素可以显著减少小鼠对 18F-FDG 的最大摄取值(SUVmax)，而 18F-FDG 的摄取与肿瘤分化程度具有相关性[39]，这都充分证明贝伐单抗联合雷帕霉素很可能成为抗肝癌血管生成的潜在疗法。在最近的研究中发现贝伐单除了增加阿霉素的化疗敏感性外，尚可降低肿瘤细胞 survivin 基因的表达[40]。对于手术无法切除肝癌的肝动脉灌注化疗中，贝伐单抗联合氟脲苷和地塞米松使用也取得了一定的治疗效果[41]。国内学者通过对 LCI-D20 高转移潜能肝癌组织原位移植裸鼠模型的研究，发现贝伐单抗抑制肝癌淋巴管形成及抑制肿瘤生长的作用时，证实贝伐单抗可有效地抑制肝癌细胞生长和淋巴管及血管的形成[42,43]。同时也研究发现抗肿瘤血管生成药贝伐单抗对 VEGF 促人肝癌细胞株 HepG2 增殖有阻断作用[44]。而且合用贝伐单抗与索拉非尼可以有效的抑制肝癌细胞的生长和转移[45]。

5. 结语

对于贝伐单抗的抗血管生成作用的研究，以及其对化学药物增敏效应的研究已经逐步成熟，对肝癌的生物化疗也取得了一定的成绩。然而对于应用贝伐单抗联合吉西他滨一线治疗转移性肝癌疗效不理想的研究[46,47]不够深入，对于贝伐单抗联合肝动脉灌注化疗栓塞治疗肝癌的研究甚少[41]，且仅为临床回顾性研究性研究而非前瞻性研究。同时这些研究都没有充分发挥贝伐单抗化疗协同作用，即：使肿瘤区血管生成正常化，减轻组织间高压，利于化疗药及氧气向肿瘤区输送，以及预防化疗所致肿瘤局部缺氧诱发 VEGF 表达的继发效应。介入治疗作为治疗晚期肝癌的首选方法，将其与贝伐单抗等抗血管生成药物联合应用时，一方面可利用化学药物通过肝动脉进入到肿瘤区直接杀死肿瘤细胞，并栓塞局部血管以减缓药物的清除，最大效能地发挥抗肿瘤抗血管生成药物的作用时效，另一方面可增强切断肿瘤灶血供和抑制肿瘤侧枝循环生成的作用[48,49]。碘化油等栓塞剂抑制新生血管生长的作用甚微，而血管生成抑制剂对已成形的血管抑制作用甚微，将二者结合可以弥补各自不足，利用栓塞剂直接阻断供血动脉及较细分支，其抑瘤作用有立竿见影的优点，同时利用血管生抑制剂从分子水平抑制微血管生长，并有效地消除栓塞剂和抗肿瘤药物引起的微环境改变所诱发的肿瘤血管新生，从而有效的阻断肿瘤血供[50]。因此对于贝伐单抗联合综合性介入治疗肝癌前瞻性的基础实验研究显得尤为重要。肝癌的综合治疗是一个长期的方向，随着生物治疗、基因治疗和综合性介入治疗等最新肝癌治疗技术的不断发展，以及对贝伐单抗、索拉非尼等抗血管生成药物研究的不断深入，相信对于肝癌的综合性治疗将从共识变为现实，科学有效的肝癌综合治疗方案将会被发现，从而将更好提高肝癌患者生存质量和远期生存率。

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