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【文献综述】

葡萄膜黑色素瘤的治疗现状

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Management status of uveal melanoma

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【Abstract】 Intra-ocular malignancy such as uveal melanoma (UM) arises from melanocytes from the uveal tract. It is paramount to detect early so as to initiate therapeutic plan as much of the survival will depend of the primary tumor size. Currently, no adjuvant therapy has demonstrated survival benefit and new insights in molecular biology, and has improved our comprehension of the pathogenesis essentially through GNAQ and GNA11 mutations and downstream signaling pathways MAPK, PI3K/Akt and Hippo, representing a multitude of therapeutic application. New research has also unfolded new range of biomarkers that could be exploited in this setting so as to improve metastasis detection. Many studies and clinical trials are ongoing.
【Key words】 uveal melanoma; management; status

【摘要】 葡萄膜黑色素瘤(uveal melanoma,UM)是起源于葡萄膜黑色素细胞的眼内恶性肿瘤。由于其生存率很大程度上取决于原发肿瘤的大小,因此早发现、早治疗非常重要。目前,UM尚无有效的辅助治疗方法。但分子生物学方面的新发现,如GNAQ和GNA11突变和涉及下游信号传导通路MAPK、PI3K/Akt和Hippo为代表的多种治疗,则有助于对UM发病机制的理解。还有研究开辟了新的生物标志物范围,以提高对UM转移的检测。此外,许多研究和临床试验也正在进行中。
【关键词】 葡萄膜黑色素瘤;治疗;现状
【中图分类号】 R773.9

葡萄膜黑色素瘤(uveal melanoma,UM)是一种罕见且在病理学上易误诊的疾病。其主要发病人群为白种成年男性[1]。在大多数情况下,该病可完全无症状,而是在常规眼科检查时发现肿瘤。UM的临床表现因肿瘤大小及位置而有所不同。该病通常需要根据病变的类型和分级,并结合对病灶生物学行为的观察来进行相应的治疗。尽管局部控制良好,但仍有50%的患者最终发生血行转移[2]。80%以上的患者会发生肝转移并导致死亡。因此,需要给予UM患者密切随访及恰当的治疗方案[3]。这需要多学科及多国合作。对于UM患者如何进行辅助治疗或转移治疗,目前尚无一致意见,而可采用的有效治疗方案不足1%[4]。现有治疗方案效率低下,尤其是对于高危患者,缺乏对转移的控制导致需要对其进行额外的化学治疗(简称化疗)[5]。通常,当UM病灶厚度小于3 mm时,医师会选择观察病情进展并对症治疗[6]。最终的治疗方案取决于医生对类似病例的经验及对利弊的权衡[7]。然而,在疾病的早期阶段,观察可能会给患者在进行主要治疗之前带来不必要的风险[8]。事实上,早发现、早治疗是延长UM患者生存期的最佳方法[9]。因此,恰当的早期治疗及合理的治疗方案是当前需要深入研究的问题[10]。

1 新辅助治疗

对UM患者进行新辅助治疗被认为能够减小肿瘤大小,并提高化疗对其治疗效果。在某些病例中,新辅助治疗成功后甚至无需手术。此外,它还能够使得手术后的病灶边缘更为清晰,特别是能够使大体积肿瘤患者的保眼治疗成为可能。通过应用血管内皮生长因子(vascular endothelial growth factor,VEGF)抑制剂来减小肿瘤的大小,不仅可减少放疗辐射的范围,也可减少放射毒性[11]。有证据表明,虽然玻璃体内应用贝伐单抗治疗UM不是常规疗法,但应用后可使近距离敷贴放疗具有良好的穿透性[12]。同时,这种治疗方案也具有争议性。有研究认为,内源性VEGF-A165b能够导致与意外组织生长相关的血管生成。此外,某些VEGF亚型能够组织细胞在体外的迁移和增殖。这些研究结果提示,VEGF抑制剂具有双重作用[12]。因此,应谨慎使用贝伐单抗治疗方案。除此之外,作为贝伐单抗治疗的一种可能性反应,UM肿瘤可以通过血管生成拟态获得微循环,这意味着需要能够靶向所涉及的分子和细胞事件的替代药物,进而干扰肿瘤灌注,控制其生长[13]。同时,优化现有药物的给药方案,探索新

的给药途径也非常重要。

2 辅助治疗

在某些情况下,只有明显转移的肿瘤患者进行化疗是有效的,为可能有残余肿瘤的患者进行手术后化疗,也被证明是有益的。其原因在于辅助治疗的目的是那些远离原发灶的微转移病灶[14]。相对于转移过程的逐渐进展,微转移灶的发展则出现得更早,此时可加强辅助全身化疗的应用。目前,在这方面还未达成共识,因此鼓励患者加入临床试验[15]。ClinicalTrials. gov 网站显示[16],有超过 60 个临床试验正在进行中,还有许多涉及 UM 治疗的临床前研究,它们都在从根本上分析能够成为现有药物潜在靶点的分子信号通路[17]。细胞毒性化疗、免疫治疗、树突状细胞疫苗、丝裂原活化蛋白激酶(mitogen-activated protein kinase,MAPK)抑制剂、组蛋白脱乙酰化酶抑制剂和低甲基化试剂是 UM 治疗的主要研究领域[18]。伊匹单抗已获 FDA 批准,但治疗对象不包括 UM 患者,回顾性和前瞻性研究表明其有一定的临床疗效[19]。与伊匹单抗相比,纳武单抗及派姆单抗具有更好的疗效且不良反应更小[19]。GNAQ/GNA11 突变在 UM 患者中普遍存在,目前许多治疗性研究旨在揭示该分子途径中可能的下游靶点,如 丁酮(也称为甲乙酮,methyl ethyl ketone,MEK)抑制剂及蛋白激酶 C(protein kinase C,PKC)抑制剂[20]。然而,其缓解率相对较低的结果令人失望[21]。目前,有许多研究正在尝试优化这一方案[22]。

在转移性黑色素瘤的治疗中,福莫司汀比达卡巴嗪等非经典烷基化剂具有更好的疗效[23]。铂类化疗药物(如顺铂)在黑色素瘤治疗中更为常用,并且已经被尝试与其他药物如他莫昔芬及舒尼替尼联合使用。它们可能具有叠加及协同作用。伊匹单抗在西班牙黑色素瘤小组-1(Spanish Melanoma Group-1,GEM-1)的Ⅱ期试验数据中显示出良好疗效,但在皮肤病合作肿瘤学组(Dermatologic Cooperative Oncology Group,DECOG)的Ⅱ期试验中的效果则不太明显[24]。克唑替尼[25]和免疫缀合物融合蛋白-1(immunoconjugate fusion protein-1,ICON-1)在抑制肿瘤转移和生长方面也显示出良好疗效[19]。新一代的 L-ICON 有望展现出类似的治疗潜力[26]。目前,尚无足够的研究结果来对这些有争议的治疗方案进行有效比较。

肝脏定向治疗也得到了广泛研究。例如,肝内切除术已被证明对 UM 转移患者有益。此外,以总体缓解率和无进展生存率为观测指标时,福莫司汀的肝动脉内给药比静脉内给药更为有效[27]。肝脏定向治疗还有一个显著优势:由于肝脏的独立性和可灌注性,使其可以最小的全身暴露进行高浓度化疗。然而,患者总体生存率并未得到改善。尽管对 UM 的化疗研究已有许多进展,但仍需研发更多药物治疗方案,同时,现有药物还需结合具体使用情况进行深入研究。

3 生物标记物

大多数 UM 是通过血行转移的。目前发现 MIA、S100-b 及骨桥蛋白与 UM 的肝转移相关[28]。如果能够分离出更多与 UM 微转移相关的生物标记物,如黑色素瘤相关转移/免疫因子,将会更有益。免疫磁珠分选法已被应用于检测 UM 循环肿瘤细胞,某些研究已经能够进行核酸定量检测,但还需要在基因组学和蛋白质组学方面进行更多研究[29]。随着 UM 的转移机制被揭示、新的分子关联被预测,UM 患者可能得到更好的分型,这意味着能够更早进行治疗以防止组织肿瘤扩散,因此前景是非常乐观的[30]。

4 结论

当前 UM 的研究旨在揭开这位神秘杀手的面纱。虽然现在的预测手段有所改进,但不能准确地评估其转移程度,因此需要诸如特异性生物标志物等新途径来检测这种变化。这将有利于开展个性化治疗。对 UM 分子水平变化的认知一方面有助于发现潜在的治疗机制,另一方面有助于改变或逆转某些病变。对现有药物的研究也在不断进行,其使用也更为谨慎。各种正在进行的临床试验结果令人乐观,针对转移的药物的研究也将为 UM 治疗带来益处。临床试验共享也非常重要,并能使患者受益。综上所述,多学科治疗、检测和个性化治疗是正确管理 UM 患者的关键。

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