·文献综述·

葡萄膜恶性黑色素瘤治疗新进展

唐 飞[1],甘 露[2],何为民[3]

作者单位:[1](611731)中国四川省成都市,四川大学华西医院上锦南府医院眼科;[2](610041)中国四川省成都市,中航工业成都363 医院眼科;[3](610041)中国四川省成都市,四川大学华西医院眼科
作者简介:唐飞,硕士,主治医师,研究方向:眼眶病。
通讯作者:何为民,博士,教授,主任医师,博士研究生导师,研究方向:眼眶病. hewm@hotmail.com
收稿日期:2016-10-13 修回日期:2016-12-27

Progress on treatment of uveal melanoma

Fei Tang[1], Lu Gan[2], Wei-Min He[3]

[1]Department of Ophthalmology, Chengdu Shangjin Nanfu Hospital, West China Hospital, S. C. U., Chengdu 611731, Sichuan Province, China; [2]Department of Ophthalmology, AVIC 363 Hospital, Chengdu 610041, Sichuan Province, China; [3]Department of Ophthalmology, West China Hospital, Sichuan University, Chengdu 610041, Sichuan Province, China.
Correspondence to: Wei-Min He. Department of Ophthalmology, West China Hospital, Sichuan University, Chengdu 610041, Sichuan Province, China. hewm@hotmail.com
Received: 2016-10-13 Accepted: 2016-12-27

Abstract

• Uveal melanoma (UM) is the most common primary intraocular malignant tumor of adult. The traditional treatment is enucleation, but it cannot completely avoid metastasis, and on the contrary, it stimulates to distant metastasis of tumor cells to some extent. According to the statistic of latest 30a, survival rates of UM patients with metastasis is still very low. Recently, many researches devoted to targeted therapy, immune therapy and radiotherapy, which have achieved gratifying results. We summarized these relative researches in this paper.

• KEYWORDS: uveal melanoma; targeted therapy; immune therapy; radiotherapy

Citation: Tang F, Gan L, He WM. Progress on treatment of uveal melanoma. *Guoji Yanke Zazhi* (*Int Eye Sci*) 2017;17(2):254-258

摘要

葡萄膜恶性黑色素瘤(uveal melanoma,UM)是成人最常见的原发性眼内恶性肿瘤。虽然目前治疗手段多种多样,眼球摘除术仍是本病的传统治疗,但手术摘除眼球并不能完全控制肿瘤的远处转移。对于伴全身转移的患者,据 30a 来的统计,生存率仍很低。近年来许多研究致力于靶向治疗、免疫治疗、放射治疗,并取得了可喜的效果,本文对相关研究进行综述。

关键词:葡萄膜恶性黑色素瘤;靶向治疗;免疫治疗;放射治疗
DOI:10.3980/j.issn.1672-5123.2017.2.15

引用:唐飞,甘露,何为民. 葡萄膜恶性黑色素瘤治疗新进展. 国际眼科杂志 2017;17(2):254-258

0 引言

葡萄膜恶性黑色素瘤(uveal melanoma,UM)是成人常见的原发性眼内恶性肿瘤,如能在肿瘤转移前诊断并局部治疗,5a 生存率大于 90%[1]。不幸的是,大约有 50% 患者诊断时已伴全身转移,最常见转移至肝脏,其次为肺,再次为骨骼[2],导致这部分患者的中位生存时间在 2~15mo[3]。传统的治疗手段包括眼球摘除、肿瘤局部切除、激光光凝。眼球摘除造成视力剥夺并影响外观;肿瘤局部切除复生率和转移率相对较高;激光光凝的有效性欠佳,临床较少使用。目前新型的治疗手段有靶向治疗、免疫治疗、放射治疗。

1 靶向治疗

靶向治疗是指以标准化的生物标记物来识别是否存在某种疾病特定的控制肿瘤生长的基因或基因谱,以此确定针对特异性靶点的治疗方法。UM 已发现的主要靶向位点有:BAP1、GNAQ/GNA11、IGF-1、VEGF 、C-kit 基因等[4]。

1.1 BAP1 BAP1(basic assembler program 1)是一个肿瘤抑制基因,编码一种组蛋白 H2A 泛素水解酶,调节细胞分化、细胞周期阻滞和 DNA 修复[5-6]。BAP1 的失活或基因突变被认为是晚期 UM 转移的重要特征,它和 UM RNA 分子经典表达Ⅱ级通路存在很强的联系,导致生存率很低[5,7-8]。组蛋白 H2A 泛素水解酶抑制剂可以扭转 BAP1 缺失对下游影响,因此具有治疗价值[5-6]。其中具有代表性的一类药物为 HDAC(类组蛋白脱乙酰酶)抑制剂,它被发现能抑制离体 UM 细胞系和活体老鼠体内肿瘤的生长,并重组编码 UM RNA 分子表型从Ⅱ型向Ⅰ型转化[9](92mo 随访生存率 UM 表型Ⅰ、Ⅱ分别为 95% 和 31%[10])。

1.2 GNAQ/GNA11 GNAQ [Guanine Nucleotide-binding protein G(q) subunit Alpha)]基因是编码异源三聚体 G 蛋白的一个 α 亚单位;GNA11 [Guanine Nucleotide-binding protein G(q) subunit Alpha-11]是 GNAQ 的旁系同源基因。二者被认为对 UM 的增生和转移具有促进作用[11]。其机制与蛋白激酶 C (protein kinase C, PKC)的活动性、丝裂原激活的蛋白激酶(mitogen activated protein kinase, MAPK)细胞信号传导通路相关[12-14]。enzastaurin,AEB071, AHT956, 作为新型的 PKC 拮抗剂,通过减少细胞外 PKC 和 MAPK 信号传导,抑制 GNAQ/

GNA11 突变,从而引起肿瘤细胞凋亡[12,14]。此外,有研究表明 PKC 拮抗剂 AEB071 与 MEK(mitogen-activated protein kinase kinase)拮抗剂 PD0325901 联合使用通过不同途径抑制 GNAQ/GNA11,能提高细胞凋亡的数量,效果优于单一用药[15]。Carvajal 等[16]进行的对照试验中发现,司美替尼(Selumetinib),通过拮抗 MAPK 间接抑制 GNAQGNAQ/GNA11 突变,与传统的化疗药物替莫唑胺(temozolomide)和达卡巴嗪(dacarbazine)相比,能提高药物反应率(response rates) 14% 和无进展生存率(progression-free survival)15.9wk。

1.3 胰岛素生长因子-1 UM 常发生肝脏转移,其发生的原因至今不明[3]。近 15a 逐渐形成的共识:肝脏分泌的生长激素有助于肿瘤向肝脏转移[17-20]。胰岛素生长因子-1(insulin-like growth factor-1,IGF-1)为其中之一,它不仅在 UM 而且在其他许多恶性肿瘤里,也起到促进肿瘤细胞增生和肿瘤发生的作用[21]。其机制为 IGF-1 发出信号传递与表皮生长因子(epidermal growth factor,EGF)结合,诱导 UM 细胞迁移和入侵,增加转移性的风险[18]。此外,IGF-1 受体(IGF-1R)不同水平的表达在许多 UM 肿瘤中也被发现[18,21]。它已成为 UM 评估预后的重要临床参数了[18-19]。目前有研究人类 UM 干细胞发现 IGF-1R 抑制剂(cyclolignan picropodophyllin,PPP),能阻碍细胞生存、增长、入侵和迁移[20,22]。有 UM 小鼠模型研究发现,在进行异种肝移植的小鼠中使用 PPP,能引起肿瘤退化降低肝脏的微转移发生[22]。Chattopadhyay 等[23]报道,一种单克隆抗体 IMC-A12 (cixutumumab)能抑制 IGF-1R,降低 IGF-1 的活动性,减少 UM 细胞的迁移。

1.4 VEGF 虽然目前系统的抗血管生成治疗在 UM 患者中未产生明显的临床反应[24-25],但血管内皮生长因子阻滞剂在动物模型中已产生部分阳性结果[26]。抗 VEGF 单克隆抗体 ranibuzimab,单一用药用于 UM 患者Ⅰ期临床试验。Bevacizumab(贝伐单抗)联合化疗药物 temozolomide(替莫唑胺)已用于 CMM 患者Ⅱ期临床试验。口服的新型抗 VEGF 药物 axitinib,作为 UM 辅助治疗药物,在Ⅱ期临床试验中近 1/3 患者部分症状得到缓解[27]。

1.5 C-kit 基因 C-kit 基因是Ⅲ类受体酪氨酸激酶家族中的一员,它能被 C-kit 干细胞因子配体活化,在血细胞生成过程中起关键作用。Kong 等[28]报道 UM 患者中 C-kit 基因发生突变比率较高。当肿瘤未发生转移时,C-kit 蛋白多呈过表达状态,而发生转移后,其表达却显著减少,其具体原因如何目前尚不可知。伊马替尼(Imatinib)是一种以 C-kit 基因为靶点的特异性酪氨酸激酶抑制剂,有研究发现伊马替尼对伴有 C-kit 突变的患者,尤其是伴有 C-kit 基因 11、13 号外显子突变患者的疗效显著,近期关于伊马替尼的Ⅱ期临床研究也在进行中[29-30]。

2 免疫治疗

UM 起源于免疫优先位点,所以部分学者猜测 UM 免疫性高于其它肿瘤,可能更易接受到免疫治疗[31]。细胞毒性 T 淋巴细胞抗原-4 (Cytotoxic T Lymphocyte Antigen 4,CTLA-4) 影响人的免疫系统,削弱其杀死癌细胞的能力。抗 CTLA-4 单抗药物 Ipilimumab 和 tremelimumab,Ipilimumab 是一种单克隆抗体,2011 年经美国 FDA 批准用于晚期黑素瘤患者[32],能有效阻滞 CTL-4,但不幸的是目前研究发现,对伴全身转移的 UM 患者的整体生存率(OR)与单纯摘除眼球的患者的 OR 没有明显提高[33-34]。Ipilimumab 被报道其临床效果并不依赖不良的预后因素(例如长期的病史和远处的转移),也不具有剂量依赖性[35-37]。Moser 等[38]所做的回顾性分析,接受 Ipilimumab 治疗的 UM 患者的中期总体生存率(median overall surviva,MOR)为 28mo 明显长于未接受 Ipilimumab 治疗组的 13mo。CTLA-4 拮抗剂 Ipilimumab,tremelimumab 治疗 CMM 患者目前仍在Ⅱ临床试验当中。也有 Ipilimumab 联合钇-90 的放射治疗研究正在进行当中[4]。关于 tremelimumab 的一个Ⅲ期临床实验表明与达卡巴嗪和替莫唑胺相比,tremelimumab 的生存获益并不明显[39]。目前我们针对抗 CTLA-4 单抗的研究还主要集中在 Ipilimumab 上,但研究报道 tremelimumab 的药物毒性、反应时间及应答率都和 Ipilimumab 相似,因而关于这两种药物的研究还应进一步深入。

程序性细胞死亡 1 受体(Programmed Death-1,PD-1)主要在激活的 T 细胞和 B 细胞中表达,功能是抑制细胞的激活,是免疫系统的一种正常的自稳机制。肿瘤微环境会诱导浸润的 T 细胞高表达 PD-1 分子,肿瘤细胞会高表达 PD-1 的配体 PD-L1 和 PD-L2,导致肿瘤微环境中 PD-1 通路持续激活,T 细胞功能被抑制,无法杀伤肿瘤细胞。PD-1 的抗体可以阻断这一通路,部分恢复 T 细胞的功能,使这些细胞能够继续杀伤肿瘤细胞。Nivolumab 和 pembrolizumab 是单克隆抗体,共同对抗 PD-1 受体在 T 细胞定位,从而减少肿瘤增生[40]。在伴全身转移的患者已证明其有效性[41-42]。

3 放射治疗

放射治疗尤其是经巩膜的敷贴短程放射治疗,已迅速成为治疗 UM 的一线治疗方式,2004/2010 年,在美国接受治疗的患者从 1.8% 猛增为 62.5%[43]。The Collaborative Ocular Melanoma Study (COMS)大样本量随机对照的研究表明,对于肿瘤为中等大小的 UM 患者,接受放射治疗的生存率与接受眼球摘除的生存率没有统计学差异。并标准化的规范了经巩膜服帖短程放射治疗[44]。由于短程敷贴放射治疗的有效性,能提供准确持续的治疗,成为近年欧美来最为广泛被用于临床治疗的方法[45]。最初的放射治疗核素钴-60,由于高能的 γ 发射对周围组织和手术人员造成伤害,已逐渐被临床淘汰[46]。低能量的 I-125、Pa-103、Ru-106 逐渐被运用,与前者比较后两者的临床经验较欠缺。放射性核素有各自的特点:I-125 的组织穿透力更强,半衰期长有助于存储,光子能量低,需要更少的屏蔽,所以肿物体积较大使推荐用,美国使用较普遍。肿物体积较小或中等大小,或靠近中央区推荐用 Ru-106,欧洲使用较普遍[47-49]。

3.1 经巩膜敷贴放射治疗 基本流程:根据眼科医生提供的肿瘤准确的位置、大小 、形状等参数选择合适的敷贴(敷贴边缘应大于肿瘤实际边缘 1~2mm)。球后麻醉后 360°剪开球结膜牵引缝合固定直肌。运用透照法标记定位,再缝合敷贴在标记的位置,最后眼表覆盖一铅遮板[40]。所以敷贴的制作至关重要。不仅可以方便放置更能有效减少放射治疗的毒副作用和对周围组织的损伤。由于 3D 技术的兴起,相对于原来的 B 超、MRI 定位,目前可以通过 3D 成像和电脑模拟技术,对后极部、

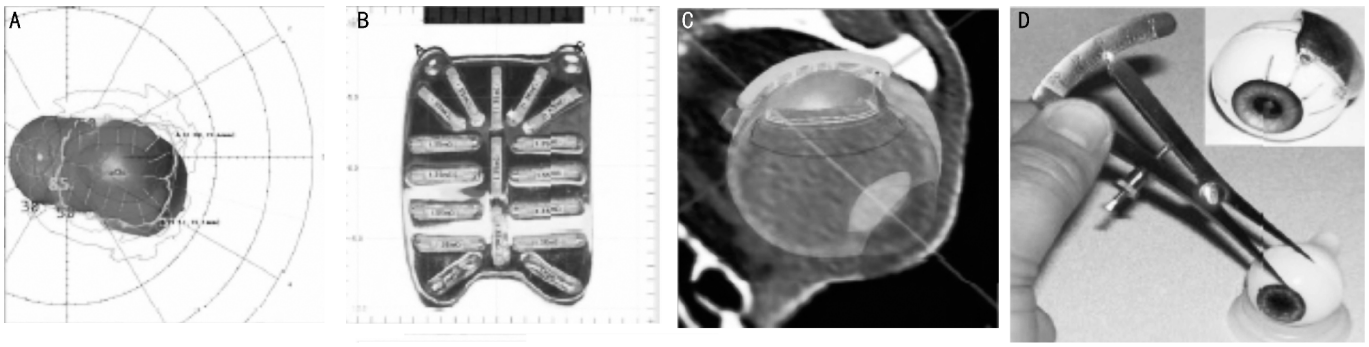

图 1　3D 成像和电脑模拟技术制作个性化的敷贴。

形态不规则、影像模糊的肿物也能准确定位,使制作的敷贴特异性更强,治疗的靶向性更准确(图 1)[50]。

COMS 试验发现,使用 I-125 短程放射治疗失败的风险(即肿瘤继续生长、复发或大量坏死扩展)很低(10.3%;95%置信区间:8.0%~13.2%)。失败的预测因素包括年龄、厚度更大的肿瘤,肿瘤邻近的黄斑区[51]。还有报道 pd-103 局部控制率也是相当高(96.7%),400 例患者中只有 14 例需要辅助后期摘除眼球[52]。另一篇回顾性分析,通过 I-125 治疗被 COMS 标准挑选的患者(肿瘤最大直径小于或等于 16mm),复发率较低(7%)[53]。目前短程放射治疗推荐的适应证[54]:高风险且不确定病变、病变厚度<10mm 和最大直径<18mm,特定被选择的较大肿物。并发症[55]:放射性视网膜病变、白内障、玻璃体出血和新生血管性青光眼等。

3.2 带电粒子放射治疗　第二个主要放射治疗葡萄膜黑色素瘤是带电粒子放射治疗(proton beam radiotherapy PBT)[56]。常用的带电粒子为质子和氦离子。由于带电离子质子和氦质子和氦离子具有布拉格峰(Bragg peak)的属性,即允许一类统一的辐射剂量在所需的深度,突然减少。因此理论上可减少对周围组织的辐射。适应证:较大肿瘤和传统敷贴不能触及的后极部肿瘤。Gragoudas 等[57]对被挑选出来接受 PBT 的 CM 患者随访观察 10a,发现肿物高度<5mm,与黄斑视盘的间距大于 2 个视盘直径的患者,75%视力大于或等于 20/200;剩余患者视力大于或等于 20/200 的仅 3%。认为影响放射治疗后视力的主要原因:肿瘤直径和高度、基础视力、视网膜脱离、糖尿病史。国外不同的文献报道接受 PBT 治疗后,肿瘤局部的复发率约 2%~5%,原因与肿瘤的大小和位置有关,同时也增加了死亡与转移的风险[57-61]。

目前有报道,低分次立体定向 PBT(总剂量 50Gy,分 5 次治疗)是一种有效的治疗中心部 UM 的方法,但仍有一定的毒性,需注意其并发症[62]。无独有偶,Desjardinsa 等[58]报道,PBT 治疗后的残余瘤可能与 PBT 的毒性作用有关,它可能产生前炎性细胞活素和 VEGF,导致眼内炎和新生血管性青光眼[63]。辅助治疗:经瞳孔温热疗法(transpupillary thermotherapy, TTT)使用一个红外二极管激光器提供低能光疗通过瞳孔较大肿瘤表面,直接引起细胞破坏导致肿瘤坏死。由于渗透性的限制,最适合治疗小病变(肿瘤高度< 3.0mm,最大基底直径< 16.0mm)[64]。但治疗的复发率高达 29%(明显高于敷贴放射治疗)[65-67]。目前仅作为 UM 放射治疗后的辅助治疗或治疗痣或不确定的病变。但 Robertson 等[66]研究报道,微小肿瘤的复发也可通过 TTT 治疗。

4 展望

随着 UM 发生机制研究的不断深入,对其致病因素、自然病程、基因表达方面认识的不断加深,传统的激光光凝、PDT 等治疗手段已逐渐淡出临床治疗,眼球摘除和敷贴放射治疗仍是目前治疗的主要手段。由于 UM 易发生转移,系统管理的综合治疗已成为医生关注的焦点。需要多学科的长期合作。也开辟一些新的治疗方向,如免疫治疗、单克隆抗体治疗、基因治疗、射频消融等。虽目前还未取得满意的效果,但能提高患者晚期的生存质量,同时各种方案的联合治疗也必将是未来治疗的发展方向。

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