WCJD 世界华人消化杂志®

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世界华人消化杂志 2017年8月28日; 25(24): 2167-2173

DOI: 10.11569/wcjd.v25.i24.2167

ISSN 1009-3079 (print) ISSN 2219-2859 (online)

述评 EDITORIAL

精准医疗时代重新审视胆管癌的诊治

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基金项目: 吉林省国际科技合作基金资助项目, No. 20160414037GH.

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收稿日期: 2017-04-28
修回日期: 2017-06-20
接受日期: 2017-06-27
在线出版日期: 2017-08-28

Diagnosis and treatment of cholangiocarcinoma in era of precision medicine

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Supported by: International Scientific and Technological Cooperation Projects of Jilin Province, No. 20160414037GH.

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Received: 2017-04-28
Revised: 2017-06-20
Accepted: 2017-06-27

Published online: 2017-08-28

Abstract

Cholangiocarcinoma (CCA) is a kind of relatively rare biliary system malignant tumor that has an extremely poor prognosis due to the lack of understanding of the molecular pathogenesis and the shortage of effective therapeutic methods. The adoption of precision medicine and cancer genomic profiling enhance our understanding of tumor molecular pathogenesis and can help identify potential therapeutic targets. Research has identified significant differences between intrahepatic and extrahepatic CCA, including epidemiology, etiology, molecular mechanisms, therapeutic methods and prognosis. The first important step towards personalized precise medicine strategy is classification of CCA and identification of the unique characteristics of each subtype. Hopefully, the acquisition and integration of omics information of CCA subtypes, and based on this, the development of effective targeted therapy will improve the prognosis and overall survival of patients.

Key Words: Intrahepatic cholangiocarcinoma; Perihilar cholangiocarcinoma; Distal cholangiocarcinoma; Molecular aberrations; Precision medicine

Sun Y, Chi BR. Diagnosis and treatment of cholangiocarcinoma in era of precision medicine. Shijie Huaren Xiaohua Zazhi 2017; 25(24): 2167-2173 URL: http://www.wjgnet.com/1009-3079/full/v25/i24/2167.htm DOI: http://dx.doi.org/10.11569/wcjd.v25.i24.2167

背景资料

胆管癌(cholangiocarcinoma, CCA)是一类相对不常见的胆管系统恶性肿瘤, 在近10年来肿瘤治疗取得进展的时代, CCA依然具有极其不良的预后, 总5年生存率<10%. 近年来研究揭示肝内、外CCA无论流行病学、病因、分子发病机制、诊治方法和预后都存在较大差异. 精准医疗计划的提出和大量分析癌症基因组数据, 有助于对肿瘤分子发病机制深入了解以及发现潜在治疗靶点.

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研发前沿

“精准医疗计划”致力于治愈癌症和糖尿病等疾病, 肿瘤在分子遗传学上的异质性和对治疗反应的差异使其成为开展实施精准医疗的最佳领域. 组学大数据时代和二代测序等生物技术的发展使获得与患者分子生物病理学、基因表达特征相匹配的个体化诊断和治疗成为可能.

摘要

胆管癌(cholangiocarcinoma, CCA)是一类相对少见的胆系恶性肿瘤. 目前极其不良的预后源于对其分子发病机制认识不足和有效治疗方法的匮乏. 精准医疗计划的提出和大量分析癌症基因组数据, 有助于对肿瘤分子发病机制深入了解以及发现潜在治疗靶点. 近年来研究证实肝内、外CCA无论流行病学、病因、分子发病机制、诊治方法和预后都存在较大差异, 将CCA按肝内CCA、肝门部CCA和远端CCA分类并深入研究各型生物学特性是迈向精准个体化医疗战略中重要的第一步. 相信随着基础和临床研究的深入, CCA各型组学信息的获得、整合和以此为据实施的精准靶向治疗, 将改善患者预后, 提高总生存率.

关键词: 肝内胆管癌; 肝门部胆管癌; 远端胆管癌; 分子变异; 精准医疗

核心提要: 将胆管癌(cholangiocarcinoma, CCA)按肝内CCA、肝门部CCA和远端CCA分类并深入研究各型生物学特性是迈向精准个体化医疗战略中重要的第一步. 随着基础和临床研究的深入, CCA各型组学信息的获得、整合和以此为据实施的精准靶向治疗, 将改善患者预后, 提高总生存率.

孙艳, 迟宝荣. 精准医疗时代重新审视胆管癌的诊治. 世界华人消化杂志 2017; 25(24): 2167-2173 URL: http://www.wjgnet.com/1009-3079/full/v25/i24/2167.htm DOI: http://dx.doi.org/10.11569/wcjd.v25.i24.2167

0 引言

胆管癌(cholangiocarcinoma, CCA)是一类相对不常见的胆管系统恶性肿瘤, 在近10年来肿瘤治疗取得进展的时代, CCA依然具有极其不良的预后, 总5年生存率<10%[1]. 目前唯一可治愈的方法仍是手术切除, 但仅约1/3的患者初诊时是可切除病灶, 且切除后的复发率也很高[2]. 至于局部晚期不可切除和复发、转移的患者更是缺乏能明显改善预后的有效措施[3]. 诊疗手段的匮乏源于对该疾病认知的不足. 精准医疗计划的提出和大量分析癌症基因组数据, 有助于对肿瘤分子发病机制深入了解以及发现潜在治疗靶点[4,5]. 精准医疗是与患者分子生物病理学特征相匹配的个体化诊断和治疗策略, 故在此新时代下重新审视CCA诊治中存在的问题、梳理该领域近期探索性基础和临床研究结果, 提出针对性合理化建议, 对提高CCA诊治、改善预后大有裨益.

1 加强CCA亚型分类

CCA是胆管系统衬覆上皮发生的恶性肿瘤的统称. 根据解剖部位不同又分为来源于肝内胆管树的肝内胆管癌(intrahepatic cholangiocarcinoma, iCCA)和肝实质以外的肝外胆管癌(extrahepatic cholangiocarcinoma, eCCA), 后者又以胆囊管与肝总管汇合点为界分为肝门部胆管癌(perihilar cholangiocarcinoma, pCCA或Klatskin瘤)和远端胆管癌(distal cholangiocarcinoma, dCCA), dCCA不包括壶腹癌. 3者发病构成比分别为iCCA 10%-20%、pCCA 50%及dCCA 30%-40%[6]. 将CCA按上述亚型分类并深入研究各型生物学特性是迈向精准个体化医疗战略中重要的第一步[7]. 究其原因如下: 既往CCA领域的研究, 如识别基因和表观遗传学变异、差异蛋白表达和组织、体液疾病生物标记等, 常将iCCA、pCCA和dCCA作为一组, 一些时候也包括胆囊癌或壶腹癌. 但近年来大量的研究[8-10]逐渐揭示肝内、外CCA无论流行病学、病因、分子发病机制、诊治方法和预后都存在较大差异.

(1)流行病学研究[11,12]显示全球范围内iCCA和eCCA具有不同的发病趋势: iCCA发病率大幅增加, 但eCCA保持稳定, 甚至轻度下降; (2)CCA细胞起源不同: iCCA可能起源于肝细胞的转分化或肝祖细胞, 然而eCCA来源于胆管上皮或胆管附属腺体, 不同的细胞来源势必具有不同的生物学特性[13-15]; (3)基因组分析[16]揭示iCCA和eCCA具有不同的体细胞突变: 二代测序技术和组学大数据分析已明确揭示CCA各亚型基因组和转录组的差异. 如近期一项最大的关于识别eCCA潜在药理靶标基因组突变分析的研究[17,18], 包括*KRAS*、*ERBB2*、*PTEN*等基因, 引人注意的是未发现异柠檬酸脱氢酶1和2(isocitrate dehydrogenase 1/2, *IDH1/2*)基因突变或表皮生长因子受体(epidermal growth factor receptor 2, *FGFR2*)基因融合, 而这两个突变被认为是iCCA中重要

的潜在靶点. 基于上述, CCA是一类高度异质性的肿瘤, 对于疑似CCA的患者, 为探索其分子发病机制、生物标记和优化治疗等, 首先应明确区分iCCA、pCCA和dCCA亚型.

2 识别CCA各亚型分子变异

CCA目前尚无治愈性的药物疗法, 也无分子靶向治疗被批准用于治疗. 发展潜在治愈性疗效的药物治疗策略受限于CCA分子和基因的异质性. 新一代测序技术时代的到来让发现潜在的靶标和可操作的分子改变成为可能. CCA精准医疗有赖于加强对各亚型包括驱动突变在内的分子和基因变异的理解.

2.1 iCCA中分子变异和靶向治疗 iCCA中值得关注的分子变异是*FGFR2*基因融合. 多项研究[19-22]显示约10%-14%的iCCA患者中存在几种不同的*FGFR2*基因融合, 如*FGFR2-BICC1*、*FGFR2-AHCYL1*、*FGFR2-TACC3*和*FGFR2-KIAA 1598*. Sia等[23]开展的一项107例iCCA患者*FGFR2*融合突变(*FGFR2-PPHLN1*、*FGFR2-BICC1*)分析显示, 高达45%(48/107)的个体有至少一种*FGFR2*基因融合. 有研究[20]表明携带*FGFR2*融合突变的iCCA具有特异的临床和病理特征, 存在*FGFR2*基因融合具有生存优势, 可能有预后意义. 但也有研究[22]显示在亚洲iCCA人群中*FGFR2*基因融合没有影响总生存、临床分期或肿瘤分化. 后续的临床前研究[24]显示在细胞和小鼠动物实验中选择性抑制*FGFR2*融合突变具有抗肿瘤疗效. 应用抑制剂针对上述突变实施精准医疗的临床试验结果也相当令人鼓舞. 一项Ⅱ期临床试验[25]应用BGJ398(一种FGFR小分子激酶抑制剂)治疗具有*FGFR2*基因融合或其他*FGFR*基因改变的既往含铂方案化疗失败的晚期CCA患者, 中期结果获得了高达82%的疾病控制率. 目前还有多项应用各种选择性或非选择性小分子激酶抑制剂和单克隆抗体精准靶向*FGFR*基因变异的Ⅰ期、Ⅱ期临床试验正在进行中[26-28], 预计陆续获得的结果将有助于提高CCA疗效.

*IDH1/2*基因突变是iCCA中另一相对频发的基因改变[29,30], iCCA中占23%-28%, 而pCCA和dCCA仅占0%-7%[31,32]. 一项94例手术切除CCA患者组织病理分析显示*IDH*突变与组织低分化相关, 在此项研究[31]中, 相比无*IDH*突变的患者, 有突变者显示具有更好的手术切除后1年生存率. 在一项326例iCCA患者的研究[33]中也观察到了*IDH*突变的良性预后意义, *IDH*突变与肿瘤切除后更长的总生存和复发时间相关. 然而, 随后的一些研究[30]提示*IDH1/2*基因突变的预后意义尚不清楚. 目前这些有关*IDH1/2*基因突变预后意义的研究结果似乎相互矛盾. 有研究者考虑到先前的研究是针对早期或可切除的病例, 而*IDH*抑制剂的靶向治疗主要用于不可切除的晚期iCCA. 因此进一步研究了104例不可切除或晚期iCCA患者*IDH*突变与预后的关系, 结果也未显示明显影响总生存[34]. 且不论*IDH1/2*基因突变是否具有预后意义, 其在几种恶性肿瘤中频发也让人推测针对此突变的抑制可能具有疗效. 目前在研的AG-221, 一种口服可利用选择性*IDH2*突变抑制剂, 已获得美国食品和药物管理局快速通道资格, 在多个Ⅰ期、Ⅱ期多中心临床实验中评估对具有*IDH2*突变包括iCCA在内的晚期实体瘤的疗效(NCT02273739).

2.2 pCCA和dCCA中分子变异和靶向治疗 相比iCCA, 有关pCCA和dCCA的研究较少. 目前多数CCA基因组分析的研究将pCCA和dCCA都归于肝外CCA组, 因此在这两种亚型识别的分子变异和潜在治疗靶点有大量重叠. 蛋白激酶A(protein kinase A, PKA)是一个依赖cAMP的蛋白激酶, PRKACA和PRKACB是PKA催化亚基, 属丝氨酸/苏氨酸蛋白激酶家族成员[35]. 近来有研究者在pCCA/dCCA中检测到PKA信号通路成员与线粒体ATP合成酶亚单位-*ATP1B*基因融合. 部分患者存在*ATP1B-PRKACA*、*ATP1B-PRKACB*基因融合, 这些融合显著的刺激*PRKACA*和*PRKACB*基因的表达以及随之下游MAPK信号通路激活[35]. 异喹啉H89是一种小分子PKA抑制剂, 已观察到能显著抑制CCA细胞的增殖[36]. ELF3编码E26转化特异的转录因子, 在多个细胞过程中对调节几个基因具有重要的作用[37]. 通过与启动子区域的相互作用ELF3提高*TGFBR2*和*EGF1*转录激活, 后二者是两个已知的抑癌基因[38]. 有研究[35]表明约9.5%的eCCA中发现*ELF3*基因突变. 功能性研究证实*ELF3*基因敲除可促进上皮细胞的运动和侵袭[39].

2.3 CCA各型共有的分子变异和靶向治疗 尽管每个CCA亚型各有独特的基因变异, 但也有一些相同的分子改变出现在所有亚型中[40-44]. 如

相关报道
肿瘤是精准医学致力的重要领域, 精准医学引领下的肺癌、胃癌、乳腺癌等肿瘤的治疗已有长足进展. 随着多种肿瘤精准医学基础和临床研究的深入, 将提高患者生存、改善预后.

创新盘点
精准医疗新时代下重新审视CCA诊治中存在的问题、梳理该领域近期探索性基础和临床研究结果, 提出针对性合理化建议, 对提高CCA诊治、改善预后大有裨益.

*K-ras*突变和PI3K-AKT-mTOR通路激活是多种肿瘤中最频发的改变, 在细胞癌变中具有重要的作用[45-47]. 原癌基因*K-ras*激活突变也是CCA中一个最常出现的基因改变. *K-ras*突变率在pCCA/dCCA中约40%, iCCA中约9%-24%[29,30]. 这些突变具有预后价值, 携带*K-ras*突变的患者显示更差的无疾病进展时间和总生存[29,48], 且更容易出现临近器官的侵袭和R1切缘状态[30]. *K-ras*激活导致包括PI3K-AKT-mTOR和Raf/MEK/ERK在内的下游效应通路的上调. 目前, 尚无直接有效的*K-ras*抑制剂, 因此针对该突变的治疗方法是抑制其下游通路. 司美替尼(selumetinib), 一种选择性*MEK1/2*抑制剂, 在治疗晚期CCA的Ⅱ期临床试验中已显示出疗效[28]. 随后应用司美替尼联合吉西他滨和顺铂治疗晚期CCA的Ⅰ期临床试验显示6.4 mon中位无疾病进展生存和可耐受的不良反应[49].

3 问题及展望

CCA虽是少发的恶性肿瘤, 但早期诊断率低, 总体预后极差. 患者总生存的提高有赖于加强对分子发病机制的认识和识别预测诊断、预后和治疗的生物标记. 大量研究已证实iCCA和eCCA在病因、分子发病机制、诊治和预后等方面存在较大差异, 因此研究CCA分子发病机制、生物标记等首先应将患者按iCCA、pCCA和dCCA分型. 纵观前期各亚型CCA的研究已获得了不少有用的数据. 但目前对发病人数居多的pCCA和dCCA认识较少, 这是今后需加强的研究领域. 再有, 发现肿瘤中驱动突变等基因异常并开展临床试验实施精准靶向治疗是提高患者生存的有效方法. 各型CCA中进行的临床试验已有不少可喜的结果, 未来需注意的是, 目前已不适宜将所有CCA患者纳入一个临床试验中, 有效精细设计的临床试验应首先将CCA患者分层, 依据解剖部位亚型、驱动基因突变和疾病分期进行分层开展的临床试验是未来发展的方向[50].

4 结论

“精准医疗计划”致力于治愈癌症和糖尿病等疾病, 肿瘤在分子遗传学上的异质性和对治疗反应的差异使其成为开展实施精准医疗的最佳领域. 组学大数据时代和二代测序等生物技术的发展使获得与患者分子生物病理学、基因表达特征相匹配的个体化诊断和治疗成为可能. 相信随着基础和临床研究的深入, iCCA、pCCA和dCCA各型组学信息的获得、整合和以此为据实施的精准靶向治疗将改善CCA患者预后, 提高总生存率.

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应用要点

肝内CCA、肝门部CCA和远端CCA各型组学信息的获得、整合和以此为据实施的精准靶向性治疗将改善CCA患者预后, 提高总生存.

名词解释

精准医疗: 与患者分子生物病理学特征相匹配的个体化诊断和治疗策略;
肝内胆管癌(iCCA): 源于肝内胆管树的胆管系统衬覆上皮发生的恶性肿瘤;
肝门部胆管癌(pCCA): 肝实质以外、胆囊管与肝总管汇合点以上的胆管系统衬覆上皮发生的恶性肿瘤;
远端胆管癌(dCCA): 胆囊管与肝总管汇合点以下的胆管系统衬覆上皮发生的恶性肿瘤.

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同行评价
本文在精准医学的大背景下, 对CCA的诊治进行了重新的分类和梳理, 为从整体上提高CCA的疗效和延长患者远期生存率带来了希望, 具有重大的临床意义和时效性.

编辑: 闫晋利 电编: 杜冉冉

ISSN 1009-3079 (print) ISSN 2219-2859 (online) DOI: 10.11569

• 消息 •

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ISSN 1009-3079