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述评 EDITORIAL

精准医疗与胰腺癌

朱世凯

■背景资料
胰腺癌是现代肿瘤学中最具挑战性的难题之一. 早期诊断和治疗是提高胰腺癌患者生存率的关键点. 随着基因组学大数据时代的来临和生物技术的迅速发展, 使得精准医疗在胰腺癌的诊断与治疗中的临床运用成为了可能.

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Role of precision medicine in pancreatic cancer

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Abstract
Pancreatic cancer is one of the most challenging problems in modern oncology. Due to difficultly in early diagnosis and early distant metastasis of pancreatic cancer, surgical resection rate is less than 20% and patients' prognosis is very poor. Despite long-term efforts taken to develop treatments for pancreatic cancer, the survival rate did not significantly improve. Therefore, early diagnosis and treatment are the key to improve the survival rate of patients with pancreatic cancer. The advent of big-data genomic era and the rapid development of biotechnology have led to the recent proposal of a new concept of precise medicine, which has quickly become the focus of world medical conferences. Here, we describe the new progress and challenges of precision medicine in pancreatic cancer, with an aim to provide new ideas for improving the survival rate of patients with pancreatic cancer.

Key Words: Pancreatic cancer; Precision medicine; Gene diagnosis; Targeted therapy

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摘要
胰腺癌是现代肿瘤学中最具挑战性的难题之一. 由于胰腺癌早期诊断极其困难, 且较

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早可发生远处转移, 手术切除率不足20%, 预后极差. 尽管对胰腺癌的诊疗经历多年的艰苦探索, 但其生存率并没有明显的提高. 因此, 早期诊断和治疗是提高胰腺癌患者生存率的关键问题所在. 随着基因组学大数据时代的来临和生物技术的迅速发展, 最近提出的精准医疗的新理念已经迅速成为全球医学界热议和高度关注的焦点. 本文阐述近些年来精准医疗理念在胰腺癌临床运用中的现状以及所面临的机遇和挑战, 为进一步提高胰腺癌患者的生存率提供新思路.

关键词: 胰腺癌; 精准医疗; 基因诊断; 靶向治疗

核心提要: 精准医疗的核心实质上就是个体化医疗, 针对每个胰腺癌患者进行精准的整合性临床分型和基因分型为指导而进行的个体化干预与治疗, 有望进一步提高胰腺癌患者的生存率.

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0 引言

精准医疗是一种与患者自身分子病理学特征相匹配的个体化诊疗的新理念[1]. 自2015年初美国总统奥巴马从国家战略层面提出“精准医疗计划”以来, 精准医疗已经迅速成为全球医学界热议和高度关注的焦点, 尤其是以精准医疗在肿瘤领域的运用最为突出[2-4].

胰腺癌是一种恶性程度最高的消化系肿瘤, 由于发病隐蔽以及特殊解剖位置, 早期诊断极其困难, 且较早可发生远处转移, 手术切除率不足20%, 预后极差, 5年总生存率低于5%. 目前, 胰腺癌仍是现代肿瘤学中最具挑战性的难题之一. 早期诊断和治疗是提高胰腺癌患者生存率的关键问题所在[5]. 近些年, 随着基因组学大数据时代的来临和生物技术的迅速发展, 使得精准医疗在胰腺癌中的临床运用成为了可能, 为进一步提高胰腺癌的诊疗水平开拓新思路[6-11].

1 胰腺癌与精准医疗

“精准医疗”的概念事实上很早就在中国的中医临床实践中有所体现. 所谓的“同病异治、异病同治”正是精准医疗的精髓所在. 随着基因组学大数据时代的来临和先进生物技术的突破[12,13], 为精准医疗在胰腺癌中的临床运用创造了良好的技术条件.

精准医疗的核心实质上就是个体化医疗, 针对每个胰腺癌患者进行精准的整合性临床分型和基因分型为指导而进行的个体化干预与治疗[14-16]. 具体上来讲, 就是通过采用二代基因测序技术对胰腺癌组织进行快速且高通量基因测序, 获取肿瘤组织大量的遗传突变信息, 结合生物信息分析和基因大数据的手段, 寻找出对胰腺癌临床诊疗有价值的突变基因, 对肿瘤进行重新的诊断和分型, 从而针对每个胰腺癌患者进行精准的干预和治疗, 以至于有望更大提高胰腺癌患者的生存率.

2 胰腺癌的早期预防

胰腺癌的早期预防更能体现出精准医疗的优势所在, 通过对有肿瘤家族史的正常人进行肿瘤遗传相关的易感癌基因评估和检测, 根据基因突变结果进行肿瘤的筛查和预防性干预与治疗, 可极大降低携带致病基因患者的患癌风险[17,18]. Wu等[19]通过对3584例胰腺癌和4868例正常人进行全基因组测序与对比分析, 结果发现中国人特有的5个染色体区域发生遗传变异包括21q21.3(BACH1)、5p13.1、21q22.3、22q13.32及10q26.11, 并且携带这5个危险基因的正常人发生胰腺癌的风险比不携带者高出6倍多. 筛选出高特异性和高精度的分子标志物是胰腺癌早期预防的必要前提, 但目前还尚未找到更多的精确标志物, 这也正是胰腺癌早期预防的难点所在, 也是当前精准医疗急需要解决的难题之一.

3 胰腺癌的早期诊断

胰腺癌的发生过程中涉及多个促癌或抑癌基因及相关信号通路的改变, 并具有广泛的时间和空间异质性. 因此, 选择高特异性和高精度的分子标志物在胰腺癌的早期诊断中同样占有非常重要地位.

糖链抗原19-9(carbohydrate antigen 19-9, CA19-9)是目前对胰腺癌早期诊断价值最高的分子标志物. CA19-9在胰腺癌患者血清中的含量明显升高, 诊断敏感性为80.3%和特异性为80.2%, 并且与临床分期呈显著正相关[20]. 但是鉴于CA19-9在胆道和结肠肿瘤以及急性胆管

研发前沿
胰腺癌的精准医疗理念旨在为患者提供与其自身分子病理学特征相匹配的精准干预与治疗手段, 以实现“因人而异、因瘤施治”的目的, 为进一步研究胰腺癌防治的新策略开拓视野.

相关报道
自2015年初美国总统奥巴马从国家战略层面提出“精准医疗计划”以来, 精准医疗已经迅速成为全球医学界热议和高度关注的焦点, 尤其是以精准医疗在肿瘤领域的运用最为突出.

炎中也会出现升高, 故单独作为胰腺癌筛选指标的意义不大[21]. 因此, CA19-9常与其他标志物联合使用以提高胰腺癌诊断的准确性.

与CA19-9相比, 最近新发现的富含细胞表面蛋白多糖-1的循环外泌体(glypican-1 circular exosomes, GPC1$^+$crExos)可能将成为是一种更可靠的胰腺癌早期诊断的新型肿瘤标志物. 这里所指的外泌体其实是一种由肿瘤细胞分泌的一种微型病毒样大小的颗粒, 其中包含绝大部分肿瘤细胞来源的DNA、RNA和蛋白质. Melo等[22]从250例胰腺癌患者血液中分离出富含GPC1$^+$crExos, 通过检测患者血液中GPC1$^+$crExos含量, 可将胰腺癌患者与健康正常人以及胰腺良性疾病患者完全区分来; 还可精确诊断早期和晚期胰腺癌, 其诊断特异性和敏感性均达100%. 更进一步研究发现早在磁共振成像尚未发现胰腺癌小鼠的肿瘤病灶时, 就可通过检测血液中GPC1$^+$crExos变化发现肿瘤的踪迹. 因此, 这结果更能证明GPC1$^+$crExos是有潜力作为胰腺癌早期诊断和筛查手段的重要成员, 并对胰腺癌精准医疗的发展具有里程碑式的意义.

*K-ras*基因同样也是一种有希望成为胰腺癌早期诊断的肿瘤标志物[23,24]. *K-ras*基因突变是胰腺癌发生早期特征性的遗传事件, 而在正常胰腺组织中极少发生[25,26]. 研究发现超过90%的胰腺癌中存在*K-ras*基因突变, 且多位于12密码子. *K-ras*基因突变引起内源性鸟苷酸三磷酸酶功能严重受损, 造成与细胞生长有关的信号通路持续活化, 进而促进胰腺癌的发生[27]. *K-ras*基因对胰腺癌诊断的敏感性为76.5%和准确性为84.5%, 但由于标本为不易获取的十二指肠液、胰液或胰腺活检组织, 所以*K-ras*基因在胰腺癌诊断方面的临床运用受到了一定限制.

近年来, 针对患者血浆游离微小RNA (microRNA, miRNA)与肿瘤早期诊断的研究也有重大突破[28]. MiRNA作为一类位于基因表达调控网络中心的重要分子, 不仅可作为一种肿瘤标志物为肿瘤的早期诊断提供依据, 而且还能为肿瘤的靶向治疗提供靶点[29-31]. 多数miRNA等被证实与胰腺癌发生发展密切相关, 在肿瘤不同阶段也有不同程度的表达, 并且稳定存在于血液、胰液等中, 使之可能成为一种稳定、方便的胰腺癌早期诊断的肿瘤标志物, 但对胰腺癌诊断的敏感性和特异性还有待进一步提高[32-34].

此外, 目前备受关注的循环血肿瘤来源游离DNA越来越多地被运用在肿瘤的检测及监测中, 在胰腺癌的早期诊断中极具发展前景[35]. 癌细胞从原发肿瘤病灶分离是显示胰腺癌发生发展的最直接指标之一. 基于患者血浆肿瘤来源的游离DNA的全基因组测序或靶向测序进行筛查分析, 可为胰腺癌的早期诊断和监测提供有力的精准医学依据[36].

4 胰腺癌的基因分型

随着新一代的基因测序和大数据技术的发展, 期待通过对胰腺癌的临床分型和基因分型进行精准整合, 以达到胰腺癌的精准医疗的目的[37]. Waddell等[38]采用二代全基因组测序将100例胰腺癌分为4种基因亚型: 稳定型、局部重排型、分散型和不稳定型. 研究发现5例因胰腺癌复发接受铂类化疗的不稳定型患者, 其中4例对化疗有反应, 而3例其他类型患者对化疗均无反应, 这表明不同亚型的基因突变对应着特定的药物靶点, 基因组拷贝数影响化疗药物的疗效. 近来, Bailey等[39]运用全基因组和深外显子测序对456例胰腺癌与其组织病理变异进行整合基因组分析, 将其分为4种亚型: 鳞状上皮型、胰腺祖细胞型、免疫原性型和异常分化的内外分泌型. 研究发现各个亚型拥有不同的生存率、治疗方法和遗传学特征. 其中鳞状上皮型肿瘤富含*TP53*和*KDM6A*基因突变、TP63转录网络的上调以及胰腺内胚层细胞的命运决定基因的甲基化, 但其预后很差, 平均生存期只有4 mo, 是其他亚型的一半. 胰腺祖细胞型肿瘤可优先表达参与胰腺早期发育基因. 内外分泌型肿瘤不仅可调控K-ras激活, 还可上调与胰腺内外分泌分化相关的基因. 免疫原性肿瘤则可上调包括获得性免疫抑制途径的免疫网络基因.

5 胰腺癌的靶向治疗

随着新一代基因测序和癌症基因组计划的突破, 使得人们深入了解肿瘤基因突变与药物治疗反应的相关性, 根据基因突变信息的整合来决定肿瘤患者的靶向治疗方案是精准医疗发展的大方向[40,41]. 目前, 已有不少的靶向药物逐步运用于胰腺癌的临床治疗.

厄洛替尼是人表皮生长因子受体(epidermal growth factor receptor, EGFR)酪氨酸激酶抑制剂, 是目前被公认可用于胰腺癌的分子靶向药物. Moore等[42]通过III期临床试验发现厄洛替尼联合吉西他滨能够明显延长胰腺癌患者的总生存期约为6.24 mo, 而吉西他滨单药组则为5.91 mo. 另外, 尼妥珠单抗也是一种以EGFR为靶点的人源化单克隆抗体药物. 经多中心的II期试验表明尼妥珠单抗联合吉西他滨治疗的胰腺癌患者较单药吉西他滨的总生存期也有一定的延长[43]. 虽然目前在胰腺癌靶向药物的研发方面取得巨大的进展[44], 但临床疗效尚不够理想, 所以仍需努力寻找更加高效和特异性的胰腺癌靶向药物.

最近, PD-1/PD-L1抑制剂在肿瘤靶向治疗领域的表现最为突出. 研究[45]发现肿瘤细胞表面表达增高的PD-L1, 与活化的T细胞上的PD-1结合, 负性调节机体的T细胞的免疫应答, 促使肿瘤细胞的逃逸. PD-1/PD-L1抑制剂能够有效阻断PD-1与PD-L1的结合, 阻断负向调控信号, 从而增强肿瘤免疫应答. PD-1/PD-L1抑制剂在多种实体肿瘤中疗效显著. PD-1抑制剂pembrolizumab和nivolumab已被美国注射用药协会批准用于临床治疗黑色素瘤和非小细胞肺癌, 而且抗PD-L1单抗MPDL3280A和MEDI4736也已进入用于治疗恶性黑色素瘤及其他实体瘤的III期临床研究. 目前, PD-1/PD-L1抑制剂在用于治疗胰腺癌的I期临床试验研究正在展开, 有希望在不久将来用于胰腺癌的靶向治疗.

近年来, 胰腺癌的精准医疗同样也聚焦在增对传统化疗药物的增效和耐药机制的研究上. 白蛋白结合型紫杉醇就是其中最为突出的代表, 其对胰腺癌的疗效远优于普通紫杉醇. 白蛋白结合型紫杉醇可经血管内皮细胞表面的9060介导跨膜转运和经肿瘤细胞外基质中的SPARC介导药物聚集, 使得药物富集肿瘤部位, 以达到杀灭胰腺癌细胞的目的. Von Hoff等[46]开展的III期临床试验研究证实接受白蛋白结合型紫杉醇联合吉西他滨治疗的胰腺癌患者总生存期明显长于吉西他滨单药组. 最近, 在胰腺癌的耐药机制方面上的研究取得了新的进展. 研究人员发现上皮细胞间质转化(epithelial-mesenchymal transition, EMT)可能参与胰腺癌耐药机制的形成, EMT能够通过抑制药物的运输和蛋白质的浓缩以及降低癌细胞的增殖, 消除抗增殖药物如吉西他滨对胰腺癌细胞的杀灭作用[47].

6 胰腺癌精准医疗的机遇与挑战

由于胰腺癌本身恶性程度极高, 加之对现有的治疗手段天然抵抗, 使得当前胰腺癌的临床治疗仍处于瓶颈阶段. 值得庆幸的是, 当前精准医疗的理念可能为胰腺癌的防治开辟一片新的天空[48]. 精准医学的核心实质上就是个体化医学. 要实现胰腺癌的精准医疗, 必须首先建立精准的临床与基础相结合的精确整合性亚型, 以此指导胰腺癌的预防、诊断和治疗. 为了实现这一目标, 各学科包括分子诊断学、生物信息学、肿瘤病理学以及临床医学等的全方位合作是成败的关键, 这是当前开展胰腺癌精准医疗的工作重点和努力和方向[49].

然而, 胰腺癌的精准医疗同样也面临着许多难题和巨大挑战, 诸如基于肿瘤的分子标志物临床诊断和分子靶向治疗组合的临床试验研究; 寻找耐药靶点制定肿瘤耐药的解决方案; 开发新的血清学基因检测方法来评估疗效、预测肿瘤复发及临床预后等[50,51]. 因此, 我们期待更多、更深入的基础研究来解决临床上遇到的这些难题, 不断丰富和完善胰腺癌精准医疗的蓝图, 为最终攻克胰腺癌提供了强有力的技术支持.

7 结论

胰腺癌是一种侵袭能力强、生存率极低的恶性肿瘤. 近些年, 尽管对胰腺癌临床诊疗的研究付出了许多努力, 但其生存率并没有明显的提高. 胰腺癌精准医疗的优势体现在于借助基因组测序获取胰腺癌大量的遗传突变信息, 经大数据分析寻找出有临床价值的突变基因, 在此基础上进行重新精确诊断与基因分型, 进而对每个胰腺癌患者进行精准的干预和治疗, 以实现“因人而异、因瘤施治”的目的.

应用要点

胰腺癌的精准医疗是借助基因组测序获取胰腺癌大量的遗传突变信息, 经大数据分析寻找出有临床价值的突变基因, 在此基础上进行重新精确诊断与分子分型, 进而对每个胰腺癌患者进行精准的干预和治疗.

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同行评价

本文阐述近些年来精准医疗理念在胰腺癌临床运用中的现状以及所面临的机遇和挑战, 评述详实、客观, 对本专业研究领域前沿掌握较好.

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