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

世界华人消化杂志®

WORLD CHINESE JOURNAL OF DIGESTOLOGY

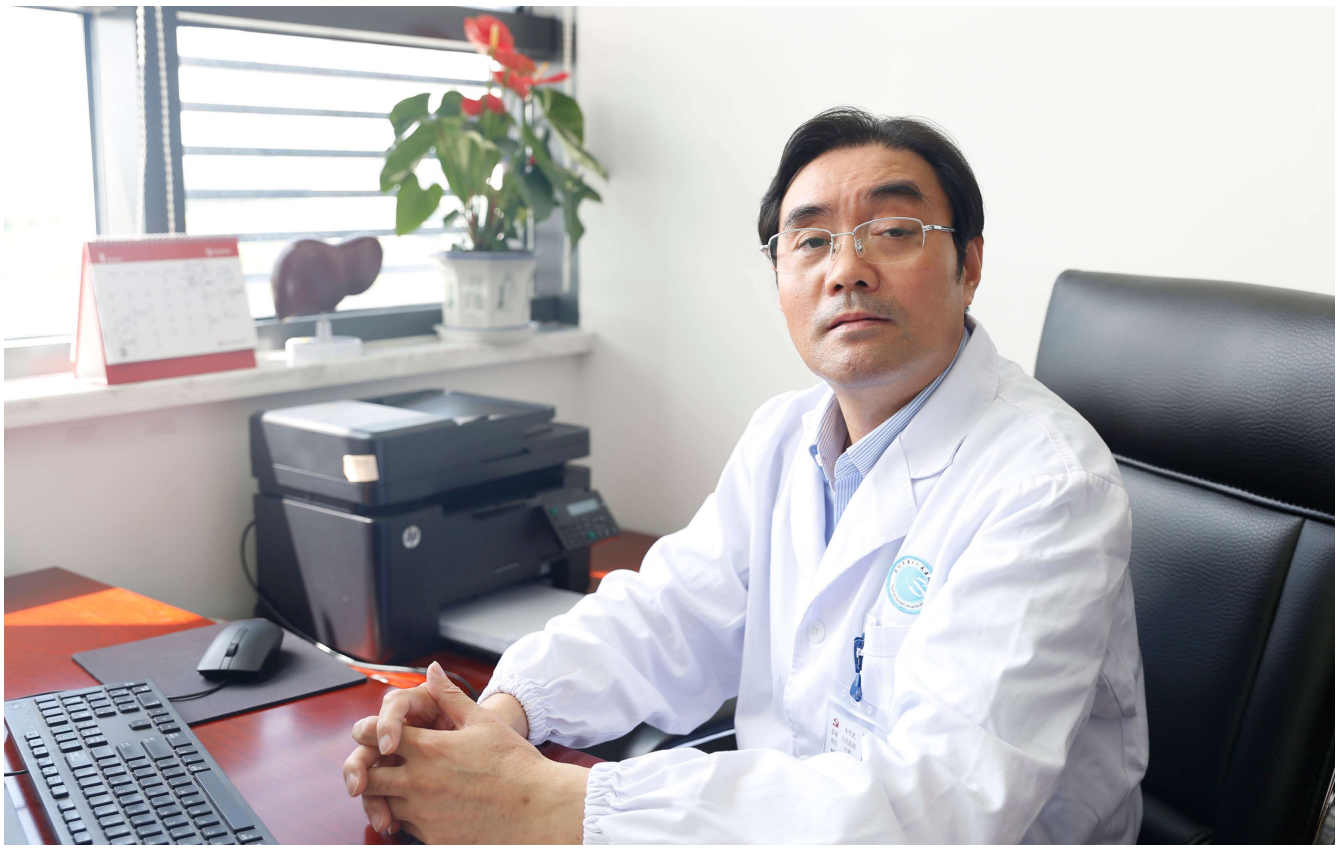
Shijie Huaren Xiaohua Zazhi

2018 年 10 月 18 日　　第 26 卷　　第 29 期　　(Volume 26 Number 29)

二零一八年十月十八日

第二十六卷

第二十九期



29/2018

ISSN 1009-3079

9 771009 307056

《世界华人消化杂志》是一本高质量的同行评议, 开放获取和在线出版的学术刊物. 本刊被美国国际检索系统《化学文摘(Chemical Abstracts, CA)》、《医学文摘库/医学文摘(EMBASE/Excerpta Medica, EM)》、《文摘杂志(Abstract Journal, AJ)》、Scopus、中国知网《中国期刊全文数据库(CNKI)》和《超星期刊域出版平台(Superstar Journals Database)》数据库收录.

WCJD 世界华人消化杂志®

目　次

2018年10月18日 第26卷 第29期 (总第613期)

述评

基础研究

临床研究

文献综述

临床实践

消　　息

封面故事

朱传武, 博士, 主任医师, 教授, 博士生导师, 苏州大学附属传染病医院感染科, 主要从事病毒性肝病的临床诊治和科研工作. 现任中国医师协会整合医学分会整合感染病防控与管理专业委员会常务委员, 中国脂肪性肝病治疗协作组委员, 江苏省中西医结合学会感染病专业委员会副主任委员、肝脏病学分会常务委员, 苏州市医学会、苏州市中西医结合学会肝病专业委员会主任委员. 主持各类科研基金资助课题20余项, 获得省、市级科技奖励10余项, 在国内外学术期刊发表论文90余篇.

本期责任人

编务 李香; 送审编辑 崔丽君; 组版编辑 张砚梁; 英文编辑 王天奇; 责任编辑 崔丽君; 形式规范审核编辑部主任 马亚娟; 最终清样审核总编辑 马连生

世界华人消化杂志

Shijie Huaren Xiaohua Zazhi

吴阶平　题写封面刊名
陈可冀　题写版权刊名

(旬刊)

创　刊 1993-01-15
改　刊 1998-01-25
出　版 2018-10-18
原刊名 新消化病学杂志

期刊名称
世界华人消化杂志

国际标准连续出版物号
ISSN 1009-3079 (print) ISSN 2219-2859 (online)

编辑部
马亚娟, 主任
《世界华人消化杂志》编辑部
Baishideng Publishing Group Inc
7901 Stoneridge Drive, Suite 501, Pleasanton, CA 94588, USA
Fax: +1-925-223-8242
Telephone: +1-925-223-8243
E-mail: wcjd@wjgnet.com
http://www.wjgnet.com

出版
百世登出版集团有限公司
Baishideng Publishing Group Inc
7901 Stoneridge Drive, Suite 501, Pleasanton, CA 94588, USA
Fax: +1-925-223-8242
Telephone: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
http://www.wjgnet.com

制作
北京百世登生物医学科技有限公司
100025, 北京市朝阳区东四环中路62号, 远洋国际中心D座903室
电话: 010-85381892
传真: 010-85381893

《世界华人消化杂志》是一本高质量的同行评议, 开放获取和在线出版的学术刊物. 本刊被美国国际检索系统《化学文摘(Chemical Abstracts, CA)》、《医学文摘库/医学文摘(EMBASE/Excerpta Medica, EM)》、《文摘杂志(Abstract Journal, AJ)》、Scopus、中国知网《中国期刊全文数据库(CNKI)》和《超星期刊域出版平台(Superstar Journals Database)》数据库收录.

《世界华人消化杂志》正式开通了在线办公系统(https://www.baishideng.com), 所有办公流程一律可以在线进行, 包括投稿、审稿、编辑、审读, 以及作者、读者和编者之间的信息反馈交流.

特别声明
本刊刊出的所有文章不代表本刊编辑部和本刊编委会的观点, 除非特别声明. 本刊如有印装质量问题, 请向本刊编辑部调换.

定价
每期90.67元 全年36期3264.00元

WCJD 世界华人消化杂志®

Contents

Volume 26 Number 29 Oct 18, 2018

EDITORIAL

BASIC RESEARCH

CLINICAL RESEARCH

REVIEW

CLINICAL PRACTICE

Contents

World Chinese Journal of Digestology
Volume 26 Number 29 Oct 18, 2018

COVER

Editorial Board Member of *World Chinese Journal of Digestology*, Chuan-Wu Zhu, Chief Physician, Professor, Department of Infectious Diseases, The Affiliated Infectious Diseases Hospital of Soochow University,10 Guangqian Road, Xiangcheng District, Suzhou 215000, Jiangsu Province, China

Indexed/Abstracted by

Chemical Abstracts, EMBASE/Excerpta Medica, Abstract Journals, Scopus, CNKI, and Superstar Journals Database.

RESPONSIBLE EDITORS FOR THIS ISSUE

Assistant Editor: *Xiang Li* Review Editor: *Li-Jun Cui* Electronic Editor: *Yan-Liang Zhang* English Language Editor: *Tian-Qi Wang* Editor-in-Charge: *Li-Jun Cui* Proof Editor: *Ya-Juan Ma* Layout Reviewer: *Lian-Sheng Ma*

Shijie Huaren Xiaohua Zazhi

Founded on January 15, 1993
Renamed on January 25, 1998
Publication date October 18, 2018

NAME OF JOURNAL
World Chinese Journal of Digestology

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

EDITORIAL OFFICE
Ya-Juan Ma, Director
World Chinese Journal of Digestology
Baishideng Publishing Group Inc
7901 Stoneridge Drive, Suite 501, Pleasanton, CA 94588, USA
Fax: +1-925-223-8242
Telephone: +1-925-223-8243
E-mail: wcjd@wjgnet.com
http://www.wjgnet.com

PUBLISHER
Baishideng Publishing Group Inc
7901 Stoneridge Drive, Suite 501, Pleasanton, CA 94588, USA
Fax: +1-925-223-8242
Telephone: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
http://www.wjgnet.com

PRODUCTION CENTER
Beijing Baishideng BioMed Scientific Co., Limited Room 903, Building D,
Ocean International Center,
No. 62 Dongsihuan Zhonglu,
Chaoyang District, Beijing 100025, China
Telephone: +86-10-85381892
Fax: +86-10-85381893

PRINT SUBSCRIPTION
RMB 90.67 Yuan for each issue
RMB 3264 Yuan for one year

WCJD 世界华人消化杂志®

在线投稿: https://www.baishideng.com

世界华人消化杂志 2018年10月18日; 26(29): 1707-1716

DOI: 10.11569/wcjd.v26.i29.1707

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

文献综述 REVIEW

肝内胆管癌的分子靶向治疗进展

奚松阳, 房 栋, 霍介格

奚松阳, 房栋, 镇江市中西医结合医院肿瘤内科 江苏省镇江市 212000

霍介格, 江苏省中西医结合医院肿瘤内科 江苏省南京市 210028

霍介格, 教授, 博士生导师, 主要从事肿瘤相关疾病的研究.

基金项目: 江苏省中医药局科技项目, No. YB201843; 江苏大学医学临床科技发展基金项目, No. JLY20160103; 第二批江苏省中医药领军人才项目, No. SLJ0211.

作者贡献分布: 本文由奚松阳与房栋撰写; 霍介格审校与修改.

通讯作者: 霍介格, 教授, 主任医师, 210028, 江苏省南京市红山路十字街100号, 江苏省中西医结合医院肿瘤内科. hjg16688@163.com
电话: 025-85637121

收稿日期: 2018-07-30
修回日期: 2018-08-24
接受日期: 2018-09-06
在线出版日期: 2018-10-18

Progress in molecular targeted therapy of intrahepatic cholangiocarcinoma

Song-Yang Xi, Dong Fang, Jie-Ge Huo

Song-Yang Xi, Dong Fang, Department of Oncology, Zhenjiang Hospital of Chinese Traditional and Western Medicine, Zhenjiang 212000, Jiangsu Province, China

Jie-Ge Huo, Department of Oncology, Jiangsu Province Hospital on Integration of Chinese and Western Medicine, Nanjing 210028, Jiangsu Province, China

Supported by: Science and Technology Project of Jiangsu Provincial Administration of Traditional Chinese Medicine, No. YB201843; Clinical Medical Science and Technology Development Fund of Jiangsu University, No. JLY20160103; the Leading Talent Project of Traditional Chinese Medicine in Jiangsu Province, No. SLJ0211.

Correspondence to: Jie-Ge Huo, Professor, Chief Physician, Department of Oncology, Jiangsu Province Hospital on Integration of Chinese and Western Medicine, 100 Shizi Street, Hongshan Road, Nanjing 210028, Jiangsu Province, China. hjg16688@163.com

Received: 2018-07-30
Revised: 2018-08-24
Accepted: 2018-09-06
Published online: 2018-10-18

Abstract

Intrahepatic cholangiocarcinoma is an uncommon malignant tumor with a poor prognosis due to an incomplete understanding of its molecular pathogenesis and a lack of effective treatment. Precision medical planning and cancer genomics can help to understand the molecular pathogenesis of cancer and identify potential therapeutic targets. With the deepening of basic and clinical research, accurate targeted therapy will be able to improve the prognosis and overall survival of patients with intrahepatic cholangiocarcinoma.

Key Words: Intrahepatic cholangiocarcinoma; Molecular targeted therapy; Molecular mechanism research; Clinical research; Precision medicine

Xi SY, Fang D, Huo JG. Progress in molecular targeted therapy of intrahepatic cholangiocarcinoma. Shijie Huaren Xiaohua Zazhi 2018; 26(29): 1707-1716 URL: http://www.wjgnet.com/1009-3079/full/v26/i29/1707.htm DOI: http://dx.doi.org/10.11569/wcjd.v26.i29.1707

摘要

肝内胆管癌是一类相对少见的恶性肿瘤. 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癌症基因组学的研究, 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. 随着基础和临床研究的深入, 精准靶向治疗将能够更好地改善患者预后, 提高总生存率.

关键词: 肝内胆管癌; 分子靶向治疗; 分子机制研究; 临床研究; 精准医学

核心提要: 肝内胆管癌(intrahepatic cholangiocarcinoma, iCCA)是一类相对少见的恶性肿瘤. 由于对于其分子发病机制认识不足并且缺乏有效的治疗方法, 肝内iCCA的预后欠佳. 但随着基础和临床研究的深入, 精准靶向治疗将能够更好地改善患者预后, 提高总生存率.

奚松阳, 房栋, 霍介格. 肝内胆管癌的分子靶向治疗进展. 世界华人消化杂志 2018; 26(29): 1707-1716 URL: http://www.wjgnet.com/1009-3079/full/v26/i29/1707.htm DOI: http://dx.doi.org/10.11569/wcjd.v26.i29.1707

0 引言

胆管癌(cholangiocarcinoma, CCA)是一种具有不同胆管细胞分化特征的上皮细胞恶性肿瘤. CCA根据解剖位置可分为肝内CCA(intrahepatic cholangiocarcinoma, iCCA), 肝门部CCA(perihilar cholangiocarcinoma, pCCA)和远端CCA(distal cholangiocarcinoma, dCCA). 每种亚型都有独特的流行病学, 生物学, 预后和临床治疗策略. 过去几十年来, 全球CCA尤其是iCCA的发病率有所增加[1]. iCCA在东亚更为常见, 在中国每10万人中有10人发病. iCCA约占所有CCA的10%, 它来自肝实质内的周围胆管, 靠近次级胆管根部. 组织学上, 大多数iCCA属于腺癌. 目前研究发现临床上只有15%患者存在手术切除的可能性, 并且中位生存期往往小于3年[2]. 对于晚期或不可切除的患者, 局部和全身化疗是主要的治疗选择, 但是疗效欠佳. 随着精准医疗计划的提出和大量癌症基因组学的研究, 对肿瘤分子发病机制的了解也不断深入, 发现了大量潜在治疗靶点, 目前国内外正在进行大量关于iCCA分子靶向治疗的临床试验, 这些研究也取得了较为可喜的成果. 本文就iCCA的分子靶向治疗进展作一阐述, 为进一步深入研究提供参考.

1 肝内胆管细胞癌的分子机制研究进展

近年来, 随着二代测序等分子检测技术的日趋完善, 一些研究采用多组学方法对iCCA的基因谱及表达谱进行了分析, 如图1所示, 发现了大量相关的基因改变[3].

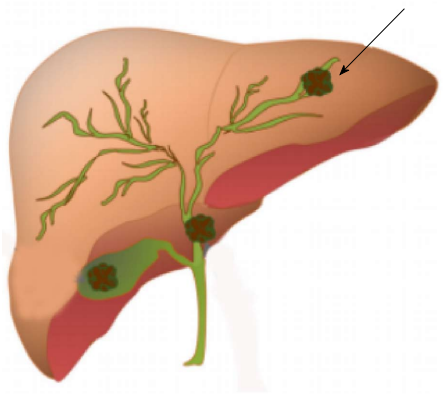
1.1 异柠檬酸脱氢酶基因突变 异柠檬酸脱氢酶(Isocitrate dehydrogenase, IDH)是参与细胞能量代谢的三羧酸循环中的限速酶, 催化异柠檬酸氧化脱羧转变为α-酮戊二酸(α-Ketoglutarate, α-KG). 针对中国103例ICC患者的肿瘤和对照样本的测序结果显示IDH1/2蛋白的基因热点突变率约占所有iCCA患者的10%-23%, 且相对肝外CCA具有高度特异性[4-6]. 目前研究发现IDH突变导致2-HG水平上调, 促使HIF1α活性增强, DNA及组蛋白处于高甲基化状态, 引起基因组高甲基化修饰的表观遗传改变和细胞的异常分化, 可能是导致iCCA发生发展的原因[7,8].

1.2 成纤维细胞生长因子受体通路 近年来, 越来越多的证据表明成纤维细胞生长因子受体(fibroblast growth factor receptor, FGFR)是某些癌症的驱动基因, 并且以“细胞自治”的方式维持肿瘤细胞的恶性特征, 通过诱导促有丝分裂和生存信号、促进肿瘤细胞侵袭转移、促进上皮间质转化、促进血管生成及参与肿瘤复发耐药作用作为癌基因参与肿瘤发生发展进程的多重步骤, 但也有研究证实FGFR信号通路在某些肿瘤类型中具有抑制肿瘤的功能[9,10]. Wu等[11]人在2013年率先报道FGFR在iCCA中的表达, 并发现2例FGFR2-BICC1蛋白的异常表达. Nakamura等[12]人对260个胆管癌 (biliary tract cancers, BTCs)患者进行了全面的基因组分析, 发现40%的病例具有靶向基因的改变, 其中FGFR2在iCCA呈现高表达.

1.3 人类表皮生长因子受体 表皮生长因子受体广泛分布于哺乳动物上皮细胞、成纤维细胞、胶质细胞、角质细胞等细胞表面, 对细胞的生长、增殖和分化等生理过程发挥重要的作用. 其在肿瘤细胞中呈现过度表达或过度活化, 可促进肿瘤细胞不断增殖, 逃避细胞凋亡, 促使肿瘤的血管生成. 表皮生长因子受体家族中与iCCA关系最为密切的是上皮生长因子受体(epidermal growth factor receptor, EGFR), 其在iCCA患者中的大多呈现过表达, 但突变一般较为罕见[13]. EGFR的活化可降低iCCA患者的总体生存, 并可提示其存在淋巴结转移的风险[14].

1.4 RAS/RAF/MEK/MAPK通路 和许多其他癌症一样, RAS/RAF/MEK/MAPK通路在CCA中常常表达异常[15]. 该通路可通过与细胞周期调节蛋白(如p53, p16 INK4A, p21 CDKN2A)相互作用调控细胞周期[16], 干预 BCL-2信号传导来逃避细胞凋亡. KRAS不仅在RAS-RAF-MEK-MAPK通路中起着重要作用, 还能影响PI3K/AKT通路, 因此具有特别重要的意义. KRAS基因在iCCA中的突变率为8.6%-24.2%[3], 且其突变与神经浸润、分期晚、预后不良有关[17]. BRAF是KRAS的下游靶点, 也易在iCCA中呈现突变[3]. BRAF突变的频率显示出相当大的地理变异性, 在德国和希腊约有20%的胆管肿瘤患者携带这种突变[18,19], 而在台湾仅有不到1%[20], 甚至在智利为0%[21].

1.5 PI3K/AKT/mTOR通路 PI3K/AKT/mTOR通路几



FGFR1-3 fusions, mutations & amplifications (11%-45%)
TPS3 mutation (2.5%-44.4%)
IDH1/2 mutation (4.9%-36%)
ARID1A mutations (6.9%-36%)
CDKN2A/B loss (5.6%-25.9%)
KRAS mutation (8.6%-24.2%)
MCL1 Amplifications (21%)
SMAD4 mutation (3.9%-16.7%)
MLL3 mutation (14.8%)
BAP1 mutation (13.0%)
PTEN mutation (0.6%-11%)
ARAF mutation (11%)
RNF43 mutation (9.3%)
ROBO2 mutation (9.3%)
GNAS mutation (9.3%)
PIK3CA mutations (3%-9%)
BRAF mutations (3%-7.1%)
ERBB3 amplification (7%)
MET amplification (2%-7%)
NRAS mutation (1.5%-7%)
CDK6 mutation (7%)
ERBB3 mutation (7%)
PEG3 mutation (5.6%)
XIRP mutation (5.6%)
RB1 mutation (5.0%)
MET mutation (4.7%)
BRCA1/2 mutation (4%)
NF1 mutation (4%)
TSC1 mutation (4%)
RADIL mutation (3.7%)
NDC80 mutation (3.7%)
PCDHA13 mutation (3.7%)
LAMA2 mutation (3.7%)
EGFR mutation (1.5%-2%)
CTNNB1 mutation (0.6%)

图 1　肝内胆管癌的基因改变.

乎在一半的恶性肿瘤中表现出过度活性, 其中就包括iCCA[14]. 和RAS-RAF-MEK通路一样, 该通路受EGF、血管内皮生长因子(vascular endothelial growth factor, VEGF)和肝细胞生长因子及受体的影响. 该通路可通过激活BCL-2并阻断caspase-9活性, 保护肿瘤细胞免于凋亡. 该途径还能促进细胞周期的进展和血管生成[22], 还有研究发现PI3K/AKT/mTOR通路参与调节基质金属蛋白酶的产生, 这在局部侵袭中起着重要作用[14]. 对101例iCCA的研究显示p-AKT1和p-mTOR的异常表达均与良性预后相关[23].

1.6 Wnt/β-catenin通路 Wnt/β-catenin通路参与了细胞侵袭和迁移的调控. 在15%iCCA的患者中, β-catenin呈现细胞核高表达细胞膜低表达[24]. Wnt通路激活与CCA异种移植肿瘤模型中的化疗耐药和转移扩散相关[25], 并且Wnt通路抑制剂可逆转细胞系中的化疗耐药[26]. 在泰国血吸虫相关CCA的突变全基因组测序研究中发现Wnt通路中RNF43基因存在9.3%的突变[27,28].

1.7 HGF/c-MET通路 c-MET被认为是侵袭性生长的关键调节基因, HGF与其受体c-MET的相互作用激活其他通路的表达, 如MAPK, PI3K/AKT和STAT等[29]. MET在iCCA中呈4-7%过表达[3], 在一些研究中已经将MET的过度表达与EGFR家族成员的过表达联系在一起[30], 并且发现HGF在iCCA迁移和侵袭中起着重要作用[31].

1.8 Hedgehog通路 研究发现在iCCA中存在Hedgehog通路相关基因的表达[32], 并且发现通过抑制Hedgehog通路在小鼠CCA异体移植瘤中的表达可抑制上皮间质转化和减少肿瘤体积[33], 表明这一通路可作为一个潜在的治疗新靶点.

1.9 炎症相关通路 炎症是iCCA发病机制中的关键因素之一. 炎性细胞因子IL-6由肿瘤细胞以自分泌或旁分泌方式响应炎症刺激而分泌, 并可影响相关癌基因的表达[13]. JAK/STAT信号的激活在iCCA占50%, 并可影响超过70%的iCCA炎症亚型[34]. IL-6与gp130受体的结合可触发受体二聚化, 导致gp130相关的JAK激酶(JAK1, JAK2和TYK2)的激活和随后的STAT3激活, 从而影响肿瘤坏死因子相关凋亡诱导配体(TRAIL)介导的细胞凋亡, 诱导细胞生长, 分化和增殖. 此外, IL-6还可增加端粒酶活性, 促进肿瘤逃避衰老, 并参与相关生长因子受体(包括EGFR)的甲基化模式, 以及参与let-7家族miRNA的表达[13].

1.10 血管生成 VEGF作为一种强有力的血管生成刺激因子, 在肿瘤相关性新血管生成中具有重要作用, 它可促进血管内皮的产生, 并引导它们向发育中的血管迁移, 为肿瘤提供氧气和营养物质, 从而促进肿瘤生长和侵袭转移[14]. 研究发现VEGF在iCCA中呈现53%的过表达, 且其表达水平与预后不良相关[13,14].

2　肝内胆管细胞癌的靶向治疗研究进展

近年来, 随着对iCCA分子病理机制认识的深入, 肿瘤生物靶向治疗发展迅速, 临床应用潜力巨大. 生物靶向治疗是针对iCCA的关键致癌靶点(抗原、受体或者基因片段), 在细胞分子水平上设计相应的治疗干预策略. 药物通过体液循环到达瘤区, 特异性结合致癌位点, 诱导肿瘤细胞坏死、凋亡或被免疫细胞吞噬, 同时不会波及肿瘤周围的正常组织细胞. 目前iCCA的分子靶向治疗

的临床研究的开展大部分包含在BTCs中, 较少进行单独的开展, 所以在部分靶向药物临床研究的介绍中以BTCs为整体进行展开(表1).

2.1 IDH基因突变 在Ⅰ期试验中, AG120(IDH1抑制剂, Agios)在具有IDH1突变的晚期实体瘤患者中表现出良好的耐受性(NCT02073994), 未呈现剂量限制性毒性. 贫血是使用AG120最常见的3级不良事件(5%). 在20例晚期iCCA患者中, 1例(5%)获得部分缓解, 11例(55%)患者疾病稳定. 在所有对AG120有反应的患者中观察到循环2-HG水平从99%降至73%, Ki67染色从96%降低至22%[3]. 其他IDH1和IDH2抑制剂最近已进入临床试验(NCT02273739, NCT02381886, NCT02481154), 并正在招募患有iCCA的患者. 最近通过包括17种BTCs在内的一大组癌细胞系的高通量药物筛选的研究发现达沙替尼对于IDH突变的iCCA具有惊人疗效[35]. 此外, 达沙替尼对IDH突变异体种植瘤的治疗中表现出明显的细胞凋亡和肿瘤消退[3]. 达沙替尼在IDH突变型晚期iCCA患者中的试验正在进行中(NCT02428855).

2.2 FGFR通路 最早报道在CCA中使用的FGFR抑制剂是BGJ-398(Infigratinib, Novartis), 其对FGFR2的半数最大抑制浓度(IC50)为1.4 mmol/L. 有34名一线化疗后FGFR异常的晚期CCA患者接受了BGJ-398Ⅱ期临床试验, 其中包括FGFR2融合28例, FGFR2突变2例, FGFR2扩增3例或FGFR3扩增1例(NCT02150967). 研究发现治疗的中位时间为188天, 客观缓解率为22%(全部8例部分缓解的患者均有FGFR2融合)[36]. 与用酪氨酸激酶抑制剂治疗的其他致癌基因引发的肿瘤一样, 获得性耐药限制了一些患者的反应耐受性. Goyal 等首次报道了3例接受BGJ398治疗的FGFR2融合阳性iCCA患者产生临床获得性FGFR抑制剂耐药[37]. 进一步研究发现FGFR2激酶结构域中的多克隆次级突变, 这其中就包括3例患者中都存在的FGFR2 V564F基因突变.

INCC54828(Incyte, NCT02924376)、BAY1163877(Bayer, NCT01976741)以及不可逆FGFR抑制剂TAS-120(Taiho, NCT02052778)等其他选择性FGFR抑制剂目前正处在包括iCCA在内的晚期实体瘤患者的早期阶段试验中[3]. 非选择性多TKIs也可针对FGFR靶点, 其中ponatinib和pazopanib已证明在对化疗产生耐药性的iCCA个别患者中表现出活性[38]. 第三种非选择性TKI ARQ-087(ARQULE, NCT0175920)目前正处在FGFR异常肿瘤包括FGFR2融合阳性的已治疗晚期iCCA患者的Ⅱ期试验中, 其可抑制RET、PDGFR、KIT、Src和FGFR1-3(FGFR2的IC50为0.68 mmol/L). 第一阶段/第二阶段初步试验数据表明用ARQ-087治疗的12例FGFR2融合阳性晚期iCCA患者中有3例有部分反应(疾病控制率为75%)[39]. 目前体外研究正在尝试研发可以克服耐药性的FGFR抑制剂为临床提供新的治疗策略.

2.3 人类表皮生长因子受体 目前几个化疗(化疗药物大部分为吉西他滨和奥沙利铂)联合靶向EGFR的单克隆抗体西妥昔单抗治疗BTCs的试验都处在Ⅱ期临床中[3]. 在一项30例的小规模研究中发现有高肿瘤缓解率(63%)[40], 虽然这个可喜的发现并未在随机Ⅱ期BINGO研究中得到证实, 但其与其他西妥昔单抗联合化疗的Ⅱ期临床研究结果一致[41].

在KRAS野生型晚期BTC患者接受帕尼单抗联合吉西他滨、卡培他滨和奥沙利铂(46例)[42], 吉西他滨和奥沙利铂(31例)[43]治疗的两项独立的Ⅱ期临床试验中, 均达到74%的6 mo PFS和45%的有效率. 但是在使用帕尼单抗联合吉西他滨和依立替康随机治疗BTC患者的Ⅱ期研究发现OS无差异(31名患者中有7名患有KRAS突变)[44]. 目前帕尼单抗联合吉西他滨和奥沙利铂的最大随机Ⅱ期研究(Vecti-BIL研究)显示85名随机患者的生存率无差异[45].

埃罗替尼在不同的研究中显示出不同的结果[3]. 在一项Ⅲ期临床研究中133名患者被随机分配接受吉西他滨和奥沙利铂化疗联合或不联合厄洛替尼, 当所有BTC患者一起分析时, PFS或OS没有差异. 然而, CCA患者似乎确实从化疗加用厄洛替尼后获益, 其中位PFS从3 mo上升至5.9 mo[46], 目前正在进行进一步的临床试验(NCT00832637、NCT00987766). 拉帕替尼目前在两个独立的Ⅱ期临床试验中疗效欠佳[3]. 曲妥珠单抗目前正在开展在胆囊癌中的Ⅱ期临床试验(NCT00478140), 在iCCA中的临床相关研究尚未开展. 阿法替尼已经在Ⅰ期临床试验中显示了在一名CCA患者中具有活性[47], 目前正在进行阿法替尼联合顺铂和吉西他滨治疗BTCs患者的Ⅰ期研究(NCT01679405).

2.4 RAS/RAF/MEK/MAPK通路 司美替尼是MEK抑制剂, 其在治疗转移性CCA的Ⅱ期研究结果显示中位PFS为3.7 mo, 中位总生存期为9.8 mo[48]. 在随后的对晚期CCA的Ib期研究中, 司美替尼、吉西他滨和顺铂的联合治疗可使中位PFS达到6.4 mo[49]. BRAF突变也可发生于CCA(主要在iCCA中), 在8例BRAF V600基因突变CCA中, 口服BRAF抑制剂维罗非尼治疗, 有1例患者取得了疗效[50].

2.5 PI3K/AKT/mTOR通路 MK-2206是AKT的抑制剂, 在8例至少接受过一次全身治疗的晚期BTCs患者的Ⅱ期临床研究中取得的结果是令人失望, 中位数PFS为1.7 mo, 中位OS为3.5 mo[51]. 依维莫司一线Ⅱ期研究显示27例患者中有14例在12 wk内实现肿瘤控制; 其

表 1 靶向药物临床研究

靶点	药物	临床研究号	临床研究
IDH基因	AG120	NCT02073994	Ⅰ期
	达沙替尼	NCT02428855	Ⅱ期
	BGJ-398	NCT02150967	Ⅱ期
	INCC54828	NCT02924376	Ⅱ期
FGFR	BAY1163877	NCT01976741	Ⅰ期
	TAS-120	NCT02052778	Ⅰ期
	ARQ-077	NCT01752920	Ⅱ期
	西妥昔单抗	NCT00552149	Ⅱ期
	帕尼单抗	NCT01308840	Ⅱ期
EGFR	厄洛替尼	NCT00832637	Ⅱ期
		NCT00987766	Ⅰ期
	拉帕替尼	NCT00107536	Ⅱ期
	阿法替尼	NCT01679405	Ⅰ期
RAS/RAF/MEK/MAPK通路	司美替尼	NCT01242605	Ⅰ期
		NCT00553332	Ⅱ期
		NCT02151084	Ⅱ期
PI3K/AKT/mTOR通路	MK-2206	NCT01859182	Ⅱ期
		NCT01425879	Ⅱ期
	依维莫司	NCT00973713	Ⅱ期
	copanlisib	NCT02631590	Ⅱ期
Wnt /β-catenin通路	DKN-01	NCT02375880	Ⅰ期
c-MET、VEGFR2	卡博替尼	NCT01954745	Ⅱ期
HGF/c-MET通路	merestinib	NCT02711553	Ⅱ期
血管生成	贝伐单抗	NCT00361231	Ⅱ期
		NCT00142480	Ⅱ期
	西地尼布	NCT00356889	Ⅱ期
		NCT00939848	Ⅱ期
	索拉非尼	NCT00955721	Ⅱ期
		NCT01093222	Ⅱ期
	厄洛替尼	NCT00661830	Ⅱ期
	舒尼替尼	NCT01093222	Ⅱ期
	凡德他尼	NCT01082809	Ⅱ期
	帕唑帕尼	NCT00753675	Ⅱ期
	瑞格菲尼	NCT01855724	Ⅱ期
		NCT02053376	Ⅱ期
	雷莫芦单抗	NCT02115542	Ⅱ期
ALK和ROS1	ceritinib	NCT02711553	Ⅱ期
	Entrectinib	NCT02374489	Ⅱ期
间皮素	Anetumab ravtansin	NCT02568267	Ⅱ期
CDK4/6	ribociclib	NCT03102320	Ⅰ期
	palbociclib	NCT03065062	Ⅰ期
PARP	niraparib	NCT02022982	Ⅰ期
		NCT03207347	Ⅱ期

中两个实现部分缓解. 中位PFS为6.0 mo、中位OS为9.5 mo[3]. PI3K抑制剂copanlisib(BAY 80-6946)一线化疗联合吉西他滨和顺铂的Ⅱ期临床试验正在进行中(NCT02631590).

2.6 Wnt/β-catenin通路 尽管目前正在开发多种Wnt通路抑制剂, 但是只有少数应用到BTCs中. Eads和他的同事们在BTCs治疗的Ⅰ期临床试验中探讨了经典Wnt/β-catenin通路抑制剂DKN-01联合吉西他滨和顺铂的疗

法是安全的, 并且可能延长了疾病的稳定时间[52].

2.7 HGF/c-MET通路 在晚期CCA患者的Ⅱ期试验中发现卡博替尼对c-MET(IC50 = 1.3 mmol/L)和VEGFR2(IC50 = 0.035 mmol/L)均有较强的活性[53]. 目前正在进行merestinib联合顺铂/吉西他滨一线药物的随机Ⅱ期研究(NCT02711553).

2.8 血管生成 在贝伐单抗联合吉西他滨和奥沙利铂的晚期BTCs Ⅱ期临床试验中发现在两个治疗周期后FDG-PET扫描的标准化摄取值显著降低, 特别是在部分缓解或稳定患者中[54]. 然而, 其6 mo PFS为63%是低于70%的目标率的. 贝伐单抗联合厄洛替尼在12%的患者中获得部分疗效, 51%的患者病情稳定, 中位OS为9.9 mo, 值得注意的是这个方案并没有同步化疗[55].

在随机Ⅱ期安慰剂对照ABC-03研究中, 我们观察到接受顺铂/吉西他滨联合西地尼布组与安慰剂组相比有效率从19%提升到44%, 并且6 mo PFS从61.3%上升至70.5%. 但是该研究并未改善中位PFS, 其原因可能与西地尼布耐受性相对较差相关[56].

其他TKIs抑制VEGF效果不佳. 在索拉非尼单药治疗[57,58]或联合厄洛替尼[59]或顺铂/吉西他滨[60]的Ⅱ临床研究中均未能发现其在BTCs中表现出足够的活性. 最近, 在随机的Ⅱ期安慰剂对照临床研究中索拉非尼吉联合西他滨后并未能改善PFS[61]. 包括56例BTCs患者在内的舒尼替尼Ⅱ期临床试验报告指出中位疾病进展时间仅为1.7 mo, 客观缓解率为8.9%, 疾病控制率为50%[62]. 在173例患者中探索凡德他尼的作用的VanGogh研究中未能显示PFS的改善[63]. 帕唑帕尼(NCT01855724), 瑞格菲尼(NCT02053376, NCT02115542)和雷莫芦单抗(NCT02711553)的临床研究尚在进行中.

2.9 其他靶点分子靶向药物 研究发现在iCCA患者中检测到涉及ROS1相关激酶ALK(EML4-ALK)的基因融合[64]. ALK和ROS1抑制剂ceritinib目前正在接受应用于ROS1阳性或ALK阳性晚期pCCA或iCCA(NCT02374489)Ⅱ期临床试验评估. Entrectinib是一种选择性酪氨酸激酶抑制剂, 具有抗ROS1和ALK(以及TRKA, TRKB和TRKC)的活性, 目前正处在涉及晚期ROS1或ALK融合的实体肿瘤患者的Ⅱ期临床研究中(NCT02568267), 其中也包括CCA在内.

间皮素是一种在非恶性间皮细胞中表达的细胞表面蛋白, 常在CCA中异常表达, 并与晚期和转移性疾病、不良的总生存期有关[65]. 因此, 这种蛋白质是治疗的潜在靶点. Anetumab ravtansine是一种抗间皮素抗体-药物结合物, 正处在招募患有异常间皮素表达的晚期CCA患者的Ⅰ期临床试验中进行试验中(NCT03102320).

CDKN2A是编码细胞周期进展的必要负调节p16INK4A和p14ARF蛋白的基因, 它在CCA中往往呈现丢失状态[12,66,67]. 这些研究显示CDK4/6抑制剂, 如ribociclib和palbociclib在治疗CCA的潜力. 这些药物目前已批准用于治疗乳腺癌, 并且正在进行一系列其他包括CCA在内的实体器官恶性肿瘤的临床试验(NCT03065062, NCT02022982).

目前研究发现肿瘤抑制基因BRCA1和BRCA2在CCA中存在突变[12,68]. BRCA突变的肿瘤通常对聚ADP核糖聚合酶(poly ADP-ribose polymerase, PARP)抑制敏感. 在18例BRCA突变CCA患者的回顾性临床分析中发现接受PARP抑制剂治疗的四名患者中有一名患者保持持续的治疗反应, PFS持续时间为42.6 mo[69]. PARP抑制剂niraparib的包括CCA在内的晚期恶性肿瘤患者Ⅱ期试验正在进行中(NCT03207347).

3 结论

iCCA虽是少发的恶性肿瘤, 但早期诊断率低, 恶性程度高, 病程进展快、手术切除率低及复发率高, 预后不佳. 目前的外科治疗主要关注在根治性切除. 由于iCCA复发率高, 为取得较好的治疗效果, 外科医生不得不一再扩大手术切除范围, 而切除范围的扩大虽延长了患者的生存时间, 但也由于削减肝功能储备的原因带来了更高的手术后并发症及手术死亡率. 目前全身性的治疗中, 可选择的方案有限, 疗效也欠佳, 且多数患者因处于晚期而无法进行化疗. 分子靶向治疗给我们带来了新的思路, 由于iCCA的形成、生长、侵袭和转移等过程由多种分子和信号转导通路参与和调控, 因而针对iCCA的靶向治疗有多种可选择的靶点, 而目前有大量相关基础研究和临床试验正在进行中, 其中部分研究已显示了较好的苗头.

尽管目前在iCCA分子机制方面的研究取得了相当大的进展, 但仍有大量的工作需要我们进一步完善. 对于正常胆管上皮细胞向侵袭性恶性肿瘤的分子改变和转化的因果关系目前尚未研究透彻. 对于产生癌细胞表型的各种信号传导途径和组分之间的相互作用我们仍不完全了解. 这些复杂的相互作用可能是加深我们对癌症异质性基础的理解和预测个体肿瘤对特定治疗的易感性的关键. 目前靶向治疗iCCA临床研究的数据和结论多来自于单臂的Ⅱ期临床试验, Ⅲ期临床研究尚无成熟的确定性结果, 仍有待于多中心、大样本、随机对照试验进一步证实靶向治疗药物的有效性与安全性.

随着大数据时代和二代测序等生物技术的发展, 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将成为可能, 精准靶向治疗将大大改善

iCCA患者预后, 提高总生存率.

4 参考文献

1 Weber SM, Ribero D, O'Reilly EM, Kokudo N, Miyazaki M, Pawlik TM. Intrahepatic cholangiocarcinoma: expert consensus statement. *HPB* (Oxford) 2015; 17: 669-680 [PMID: 26172134 DOI: 10.1111/hpb.12441]

2 Buettner S, van Vugt JL, IJzermans JN, Groot Koerkamp B. Intrahepatic cholangiocarcinoma: current perspectives. *Onco Targets Ther* 2017; 10: 1131-1142 [PMID: 28260927 DOI: 10.2147/OTT.S93629]

3 Valle JW, Lamarca A, Goyal L, Barriuso J, Zhu AX. New Horizons for Precision Medicine in Biliary Tract Cancers. *Cancer Discov* 2017; 7: 943-962 [PMID: 28818953 DOI: 10.1158/2159-8290.CD-17-0245]

4 Zou S, Li J, Zhou H, Frech C, Jiang X, Chu JS, Zhao X, Li Y, Li Q, Wang H, Hu J, Kong G, Wu M, Ding C, Chen N, Hu H. Mutational landscape of intrahepatic cholangiocarcinoma. *Nat Commun* 2014; 5: 5696 [PMID: 25526346 DOI: 10.1038/ncomms6696]

5 Clark O, Yen K, Mellinghoff IK. Molecular Pathways: Isocitrate Dehydrogenase Mutations in Cancer. *Clin Cancer Res* 2016; 22: 1837-1842 [PMID: 26819452 DOI: 10.1158/1078-0432.CCR-13-1333]

6 Razumilava N, Gores GJ. Cholangiocarcinoma. *Lancet* 2014; 383: 2168-2179 [PMID: 24581682 DOI: 10.1016/S0140-6736(13)61903-0]

7 魏妙艳, 汤朝晖, 全志伟. 代谢在肝内胆管癌发病机制及临床诊治中的研究进展. 世界华人消化杂志 2017; 25: 2929-2937 [DOI: 10.11569/wcjd.v25.i33.2929]

8 Saha SK, Parachoniak CA, Ghanta KS, Fitamant J, Ross KN, Najem MS, Gurumurthy S, Akbay EA, Sia D, Cornella H, Miltiadous O, Walesky C, Deshpande V, Zhu AX, Hezel AF, Yen KE, Straley KS, Travins J, Popovici-Muller J, Gliser C, Ferrone CR, Apte U, Llovet JM, Wong KK, Ramaswamy S, Bardeesy N. Mutant IDH inhibits HNF-4α to block hepatocyte differentiation and promote biliary cancer. *Nature* 2014; 513: 110-114 [PMID: 25043045 DOI: 10.1038/nature13441]

9 Taylor JG 6th, Cheuk AT, Tsang PS, Chung JY, Song YK, Desai K, Yu Y, Chen QR, Shah K, Youngblood V, Fang J, Kim SY, Yeung C, Helman LJ, Mendoza A, Ngo V, Staudt LM, Wei JS, Khanna C, Catchpoole D, Qualman SJ, Hewitt SM, Merlino G, Chanock SJ, Khan J. Identification of FGFR4-activating mutations in human rhabdomyosarcomas that promote metastasis in xenotransplanted models. *J Clin Invest* 2009; 119: 3395-3407 [PMID: 19809159 DOI: 10.1172/JCI39703]

10 Repana D, Ross P. Targeting FGF19/FGFR4 Pathway: A Novel Therapeutic Strategy for Hepatocellular Carcinoma. *Diseases* 2015; 3: 294-305 [PMID: 28943626 DOI: 10.3390/diseases3040294]

11 Wu YM, Su F, Kalyana-Sundaram S, Khazanov N, Ateeq B, Cao X, Lonigro RJ, Vats P, Wang R, Lin SF, Cheng AJ, Kunju LP, Siddiqui J, Tomlins SA, Wyngaard P, Sadis S, Roychowdhury S, Hussain MH, Feng FY, Zalupski MM, Talpaz M, Pienta KJ, Rhodes DR, Robinson DR, Chinnaiyan AM. Identification of targetable FGFR gene fusions in diverse cancers. *Cancer Discov* 2013; 3: 636-647 [PMID: 23558953 DOI: 10.1158/2159-8290.CD-13-0050]

12 Nakamura H, Arai Y, Totoki Y, Shirota T, Elzawahry A, Kato M, Hama N, Hosoda F, Urushidate T, Ohashi S, Hiraoka N, Ojima H, Shimada K, Okusaka T, Kosuge T, Miyagawa S, Shibata T. Genomic spectra of biliary tract cancer. *Nat Genet* 2015; 47: 1003-1010 [PMID: 26258846 DOI: 10.1038/ng.3375]

13 Sia D, Tovar V, Moeini A, Llovet JM. Intrahepatic cholangiocarcinoma: pathogenesis and rationale for molecular therapies. *Oncogene* 2013; 32: 4861-4870 [PMID: 23318457 DOI: 10.1038/onc.2012.617]

14 Marks EI, Yee NS. Molecular genetics and targeted therapeutics in biliary tract carcinoma. *World J Gastroenterol* 2016; 22: 1335-1347 [PMID: 26819503 DOI: 10.3748/wjg.v22.i4.1335]

15 O'Neill E, Kolch W. Conferring specificity on the ubiquitous Raf/MEK signalling pathway. *Br J Cancer* 2004; 90: 283-288 [PMID: 14735164 DOI: 10.1038/sj.bjc.6601488]

16 McCubrey JA, Steelman LS, Chappell WH, Abrams SL, Wong EW, Chang F, Lehmann B, Terrian DM, Milella M, Tafuri A, Stivala F, Libra M, Basecke J, Evangelisti C, Martelli AM, Franklin RA. Roles of the Raf/MEK/ERK pathway in cell growth, malignant transformation and drug resistance. *Biochim Biophys Acta* 2007; 1773: 1263-1284 [PMID: 17126425 DOI: 10.1016/j.bbamcr.2006.10.001]

17 Chen TC, Jan YY, Yeh TS. K-ras mutation is strongly associated with perineural invasion and represents an independent prognostic factor of intrahepatic cholangiocarcinoma after hepatectomy. *Ann Surg Oncol* 2012; 19: S675-S681 [PMID: 22290568 DOI: 10.1245/s10434-012-2224-7]

18 Tannapfel A, Sommerer F, Benicke M, Katalinic A, Uhlmann D, Witzigmann H, Hauss J, Wittekind C. Mutations of the BRAF gene in cholangiocarcinoma but not in hepatocellular carcinoma. *Gut* 2003; 52: 706-712 [PMID: 12692057]

19 Saetta AA, Papanastasiou P, Michalopoulos NV, Gigelou F, Korkolopoulou P, Bei T, Patsouris E. Mutational analysis of BRAF in gallbladder carcinomas in association with K-ras and p53 mutations and microsatellite instability. *Virchows Arch* 2004; 445: 179-182 [PMID: 15221372 DOI: 10.1007/s00428-004-1046-9]

20 Chang YT, Chang MC, Huang KW, Tung CC, Hsu C, Wong JM. Clinicopathological and prognostic significances of EGFR, KRAS and BRAF mutations in biliary tract carcinomas in Taiwan. *J Gastroenterol Hepatol* 2014; 29: 1119-1125 [PMID: 24372748 DOI: 10.1111/jgh.12505]

21 Goldenberg D, Rosenbaum E, Argani P, Wistuba II, Sidransky D, Thuluvath PJ, Hidalgo M, Califano J, Maitra A. The V599E BRAF mutation is uncommon in biliary tract cancers. *Mod Pathol* 2004; 17: 1386-1391 [PMID: 15181454 DOI: 10.1038/modpathol.3800204]

22 Zoncu R, Efeyan A, Sabatini DM. mTOR: from growth signal integration to cancer, diabetes and ageing. *Nat Rev Mol Cell Biol* 2011; 12: 21-35 [PMID: 21157483 DOI: 10.1038/nrm3025]

23 Lee D, Do IG, Choi K, Sung CO, Jang KT, Choi D, Heo JS, Choi SH, Kim J, Park JY, Cha HJ, Joh JW, Choi KY, Kim DS. The expression of phospho-AKT1 and phospho-MTOR is associated with a favorable prognosis independent of PTEN expression in intrahepatic cholangiocarcinomas. *Mod Pathol* 2012; 25: 131-139 [PMID: 21874010 DOI: 10.1038/modpathol.2011.133]

24 Settakorn J, Kaewpila N, Burns GF, Leong AS. FAT, E-cadherin, beta catenin, HER 2/neu, Ki67 immunoexpression, and histological grade in intrahepatic cholangiocarcinoma. *J Clin Pathol* 2005; 58: 1249-1254 [PMID: 16311342 DOI: 10.1136/jcp.2005.026575]

25 Wang W, Zhong W, Yuan J, Yan C, Hu S, Tong Y, Mao Y, Hu T, Zhang B, Song G. Involvement of Wnt/β-catenin signaling in the mesenchymal stem cells promote metastatic growth and chemoresistance of cholangiocarcinoma. *Oncotarget* 2015; 6: 42276-42289 [PMID: 26474277 DOI: 10.18632/oncotarget.5514]

26 Shen DY, Zhang W, Zeng X, Liu CQ. Inhibition of Wnt/β-catenin signaling downregulates P-glycoprotein and reverses multi-drug resistance of cholangiocarcinoma. *Cancer Sci* 2013; 104: 1303-1308 [PMID: 23822562 DOI: 10.1111/cas.12223]

27 Ong CK, Subimerb C, Pairojkul C, Wongkham S, Cutcutache I, Yu W, McPherson JR, Allen GE, Ng CC, Wong BH, Myint SS, Rajasegaran V, Heng HL, Gan A, Zang ZJ, Wu Y, Wu J, Lee MH, Huang D, Ong P, Chan-on W, Cao Y, Qian CN, Lim KH, Ooi A, Dykema K, Furge K, Kukongviriyapan V, Sripa B, Wongkham C, Yongvanit P, Futreal PA, Bhudhisawasdi V, Rozen S, Tan P, Teh BT. Exome sequencing of liver fluke-associated cholangiocarcinoma. *Nat Genet* 2012; 44: 690-693 [PMID: 22561520 DOI: 10.1038/ng.2273]

28 Jusakul A, Kongpetch S, Teh BT. Genetics of Opisthorchis viverrini-related cholangiocarcinoma. *Curr Opin Gastroenterol* 2015; 31: 258-263 [PMID: 25693006 DOI: 10.1097/MOG.0000000000000162]

29 Comoglio PM, Giordano S, Trusolino L. Drug development of MET inhibitors: targeting oncogene addiction and expedience. *Nat Rev Drug Discov* 2008; 7: 504-516 [PMID: 18511928 DOI: 10.1038/nrd2530]

30 Miyamoto M, Ojima H, Iwasaki M, Shimizu H, Kokubu A, Hiraoka N, Kosuge T, Yoshikawa D, Kono T, Furukawa H, Shibata T. Prognostic significance of overexpression of c-Met oncoprotein in cholangiocarcinoma. *Br J Cancer* 2011; 105: 131-138 [PMID: 21673683 DOI: 10.1038/bjc.2011.199]

31 Leelawat K, Leelawat S, Tepaksorn P, Rattanasinganchan P, Leungchaweng A, Tohtong R, Sobhon P. Involvement of c-Met/hepatocyte growth factor pathway in cholangiocarcinoma cell invasion and its therapeutic inhibition with small interfering RNA specific for c-Met. *J Surg Res* 2006; 136: 78-84 [PMID: 16950403 DOI: 10.1016/j.jss.2006.05.031]

32 Tang L, Tan YX, Jiang BG, Pan YF, Li SX, Yang GZ, Wang M, Wang Q, Zhang J, Zhou WP, Dong LW, Wang HY. The prognostic significance and therapeutic potential of hedgehog signaling in intrahepatic cholangiocellular carcinoma. *Clin Cancer Res* 2013; 19: 2014-2024 [PMID: 23493353 DOI: 10.1158/1078-0432.CCR-12-0349]

33 Riedlinger D, Bahra M, Boas-Knoop S, Lippert S, Bradtmöller M, Guse K, Seehofer D, Bova R, Sauer IM, Neuhaus P, Koch A, Kamphues C. Hedgehog pathway as a potential treatment target in human cholangiocarcinoma. *J Hepatobiliary Pancreat Sci* 2014; 21: 607-615 [PMID: 24733827 DOI: 10.1002/jhbp.107]

34 Sia D, Hoshida Y, Villanueva A, Roayaie S, Ferrer J, Tabak B, Peix J, Sole M, Tovar V, Alsinet C, Cornella H, Klotzle B, Fan JB, Cotsoglou C, Thung SN, Fuster J, Waxman S, Garcia-Valdecasas JC, Bruix J, Schwartz ME, Beroukhim R, Mazzaferro V, Llovet JM. Integrative molecular analysis of intrahepatic cholangiocarcinoma reveals 2 classes that have different outcomes. *Gastroenterology* 2013; 144: 829-840 [PMID: 23295441 DOI: 10.1053/j.gastro.2013.01.001]

35 Saha SK, Gordan JD, Kleinstiver BP, Vu P, Najem MS, Yeo JC, Shi L, Kato Y, Levin RS, Webber JT, Damon LJ, Egan RK, Greninger P, McDermott U, Garnett MJ, Jenkins RL, Rieger-Christ KM, Sullivan TB, Hezel AF, Liss AS, Mizukami Y, Goyal L, Ferrone CR, Zhu AX, Joung JK, Shokat KM, Benes CH, Bardeesy N. Isocitrate Dehydrogenase Mutations Confer Dasatinib Hypersensitivity and SRC Dependence in Intrahepatic Cholangiocarcinoma. *Cancer Discov* 2016; 6: 727-739 [PMID: 27231123 DOI: 10.1158/2159-8290.CD-15-1442]

36 Javle MM, Shroff RT, Zhu A, Sadeghi S, Choo SP, Borad MJ, Lowery MA,El-Khoueiry A, Macarulla T, Philip PA. A phase 2 study of BGJ398 in patients (pts) with advanced or metastatic FGFR-altered cholangiocarcinoma (CCA) who failed or are intolerant to platinum-based chemotherapy. *J Clin Oncol* 2016; 34: 33 [DOI: 10.1200/jco.2016.34.4_suppl.335]

37 Goyal L, Saha SK, Liu LY, Siravegna G, Leshchiner I, Ahronian LG, Lennerz JK, Vu P, Deshpande V, Kambadakone A, Mussolin B, Reyes S, Henderson L, Sun JE, Van Seventer EE, Gurski JM Jr, Baltschukat S, Schacher-Engstler B, Barys L, Stamm C, Furet P, Ryan DP, Stone JR, Iafrate AJ, Getz G, Porta DG, Tiedt R, Bardelli A, Juric D, Corcoran RB, Bardeesy N, Zhu AX. Polyclonal Secondary FGFR2 Mutations Drive Acquired Resistance to FGFR Inhibition in Patients with FGFR2 Fusion-Positive Cholangiocarcinoma. *Cancer Discov* 2017; 7: 252-263 [PMID: 28034880 DOI: 10.1158/2159-8290.CD-16-1000]

38 Borad MJ, Champion MD, Egan JB, Liang WS, Fonseca R, Bryce AH, McCullough AE, Barrett MT, Hunt K, Patel MD, Young SW, Collins JM, Silva AC, Condjella RM, Block M, McWilliams RR, Lazaridis KN, Klee EW, Bible KC, Harris P, Oliver GR, Bhavsar JD, Nair AA, Middha S, Asmann Y, Kocher JP, Schahl K, Kipp BR, Barr Fritcher EG, Baker A, Aldrich J, Kurdoglu A, Izatt T, Christoforides A, Cherni I, Nasser S, Reiman R, Phillips L, McDonald J, Adkins J, Mastrian SD, Placek P, Watanabe AT, Lobello J, Han H, Von Hoff D, Craig DW, Stewart AK, Carpten JD. Integrated genomic characterization reveals novel, therapeutically relevant drug targets in FGFR and EGFR pathways in sporadic intrahepatic cholangiocarcinoma. *PLoS Genet* 2014; 10: e1004135 [PMID: 24550739 DOI: 10.1371/journal.pgen.1004135]

39 Mazzaferro V, Shaib W, Rimassa L, Harris W, Personeni N, El-Rayes B, Tolcher A, Hall T, Wang Y, Schwartz B, Kazakin J, Droz Dit Busset M, Cotsoglou C, Papadopoulos K. ARQ 087, an oral pan- fibroblast growth factor receptor (FGFR) inhibitor, in patients (pts) with advanced and/or metastatic intrahepatic cholangiocarcinoma (iCCA). *Ann oncol* 2016; 27: ii109.1-ii109 [DOI: 10.1093/annonc/mdw200.19]

40 Gruenberger B, Schueller J, Heubrandtner U, Wrba F, Tamandl D, Kaczirek K, Roka R, Freimann-Pircher S, Gruenberger T. Cetuximab, gemcitabine, and oxaliplatin in patients with unresectable advanced or metastatic biliary tract cancer: a phase 2 study. *Lancet Oncol* 2010; 11: 1142-1148 [PMID: 21071270 DOI: 10.1016/S1470-2045(10)70247-3]

41 Malka D, Cervera P, Foulon S, Trarbach T, de la Fouchardière C, Boucher E, Fartoux L, Faivre S, Blanc JF, Viret F, Assenat E, Seufferlein T, Herrmann T, Grenier J, Hammel P, Dollinger M, André T, Hahn P, Heinemann V, Rousseau V, Ducreux M, Pignon JP, Wendum D, Rosmorduc O, Greten TF; BINGO investigators. Gemcitabine and oxaliplatin with or without cetuximab in advanced biliary-tract cancer (BINGO): a randomised, open-label, non-comparative phase 2 trial. *Lancet Oncol* 2014; 15: 819-828 [PMID: 24852116 DOI: 10.1016/S1470-2045(14)70212-8]

42 Jensen LH, Lindebjerg J, Ploen J, Hansen TF, Jakobsen A. Phase II marker-driven trial of panitumumab and chemotherapy in KRAS wild-type biliary tract cancer. *Ann Oncol* 2012; 23: 2341-2346 [PMID: 22367707 DOI: 10.1093/annonc/mds008]

43 Hezel AF, Noel MS, Allen JN, Abrams TA, Yurgelun M, Faris JE, Goyal L, Clark JW, Blaszkowsky LS, Murphy JE, Zheng H, Khorana AA, Connolly GC, Hyrien O, Baran A, Herr M, Ng K, Sheehan S, Harris DJ, Regan E, Borger DR, Iafrate AJ, Fuchs C, Ryan DP, Zhu AX. Phase II study of gemcitabine, oxaliplatin in combination with panitumumab in KRAS wild-type unresectable or metastatic biliary tract and gallbladder cancer. *Br J Cancer* 2014; 111: 430-436 [PMID: 24960403 DOI: 10.1038/bjc.2014.343]

44 Sohal DP, Mykulowycz K, Uehara T, Teitelbaum UR, Damjanov N, Giantonio BJ, Carberry M, Wissel P, Jacobs-Small M, O'Dwyer PJ, Sepulveda A, Sun W. A phase II trial of gemcitabine, irinotecan and panitumumab in advanced cholangiocarcinoma. *Ann Oncol* 2013; 24: 3061-3065 [PMID:

24146220 DOI: 10.1093/annonc/mdt416]
45 Leone F, Marino D, Cereda S, Filippi R, Belli C, Spadi R, Nasti G, Montano M, Amatu A, Aprile G, Cagnazzo C, Fasola G, Siena S, Ciuffreda L, Reni M, Aglietta M. Panitumumab in combination with gemcitabine and oxaliplatin does not prolong survival in wild-type KRAS advanced biliary tract cancer: A randomized phase 2 trial (Vecti-BIL study). *Cancer* 2016; 122: 574-581 [PMID: 26540314 DOI: 10.1002/cncr.29778]
46 Lee J, Park SH, Chang HM, Kim JS, Choi HJ, Lee MA, Jang JS, Jeung HC, Kang JH, Lee HW, Shin DB, Kang HJ, Sun JM, Park JO, Park YS, Kang WK, Lim HY. Gemcitabine and oxaliplatin with or without erlotinib in advanced biliary-tract cancer: a multicentre, open-label, randomised, phase 3 study. *Lancet Oncol* 2012; 13: 181-188 [PMID: 22192731 DOI: 10.1016/S1470-2045(11)70301-1]
47 Suder A, Ang JE, Kyle F, Harris D, Rudman S, Kristeleit R, Solca F, Uttenreuther-Fischer M, Pemberton K, Pelling K, Schnell D, de Bono J, Spicer J. A phase I study of daily afatinib, an irreversible ErbB family blocker, in combination with weekly paclitaxel in patients with advanced solid tumours. *Eur J Cancer* 2015; 51: 2275-2284 [PMID: 26296295 DOI: 10.1016/j.ejca.2015.07.041]
48 Bekaii-Saab T, Phelps MA, Li X, Saji M, Goff L, Kauh JS, O'Neil BH, Balsom S, Balint C, Liersemann R, Vasko VV, Bloomston M, Marsh W, Doyle LA, Ellison G, Grever M, Ringel MD, Villalona-Calero MA. Multi-institutional phase II study of selumetinib in patients with metastatic biliary cancers. *J Clin Oncol* 2011; 29: 2357-2363 [PMID: 21519026 DOI: 10.1200/JCO.2010.33.9473]
49 Bridgewater J, Lopes A, Beare S, Duggan M, Lee D, Ricamara M, McEntee D, Sukumaran A, Wasan H, Valle JW. A phase 1b study of Selumetinib in combination with Cisplatin and Gemcitabine in advanced or metastatic biliary tract cancer: the ABC-04 study. *BMC Cancer* 2016; 16: 153 [PMID: 26912134 DOI: 10.1186/s12885-016-2174-8]
50 Rizvi S, Khan SA, Hallemeier CL, Kelley RK, Gores GJ. Cholangiocarcinoma - evolving concepts and therapeutic strategies. *Nat Rev Clin Oncol* 2018; 15: 95-111 [PMID: 28994423 DOI: 10.1038/nrclinonc.2017.157]
51 Ahn DH, Li J, Wei L, Doyle A, Marshall JL, Schaaf LJ, Phelps MA, Villalona-Calero MA, Bekaii-Saab T. Results of an abbreviated phase-II study with the Akt Inhibitor MK-2206 in Patients with Advanced Biliary Cancer. *Sci Rep* 2015; 5: 12122 [PMID: 26161813 DOI: 10.1038/srep12122]
52 Eads J, Stein S, El-Khoueiry A, Manji G, Abrams T, Khorana AA, Miksad R, Mahalingam D, Sirard C, Zhu AX, Goyal L. Phase I study of DKN-01, an anti-DKK1 antibody, in combination with gemcitabine (G) and cisplatin (C) in patients (pts) with advanced biliary cancer. *Ann Oncol* 2016; 27 [DOI: 10.1093/annonc/mdw371.90]
53 Goyal L, Yurgelun MB, Abrams TA, Kwak EL, Cleary JM, Knowles M, Regan E, Gisondi A, Sheehan S, Zheng H, Zhu AX. A Phase II trial of Cabozantinib (XL-184) in Patients with Advanced Cholangiocarcinoma. *J Clin Oncol* 2015; 33: 800 [DOI: 10.1200/jco.2015.33.3_suppl.800]
54 Zhu AX, Meyerhardt JA, Blaszkowsky LS, Kambadakone AR, Muzikansky A, Zheng H, Clark JW, Abrams TA, Chan JA, Enzinger PC, Bhargava P, Kwak EL, Allen JN, Jain SR, Stuart K, Horgan K, Sheehan S, Fuchs CS, Ryan DP, Sahani DV. Efficacy and safety of gemcitabine, oxaliplatin, and bevacizumab in advanced biliary-tract cancers and correlation of changes in 18-fluorodeoxyglucose PET with clinical outcome: a phase 2 study. *Lancet Oncol* 2010; 11: 48-54 [PMID: 19932054 DOI: 10.1016/S1470-2045(09)70333-X]
55 Lubner SJ, Mahoney MR, Kolesar JL, Loconte NK, Kim GP, Pitot HC, Philip PA, Picus J, Yong WP, Horvath L, Van Hazel G, Erlichman CE, Holen KD. Report of a multicenter phase II trial testing a combination of biweekly bevacizumab and daily erlotinib in patients with unresectable biliary cancer: a phase II Consortium study. *J Clin Oncol* 2010; 28: 3491-3497 [PMID: 20530271 DOI: 10.1200/JCO.2010.28.4075]
56 Valle JW, Wasan H, Lopes A, Backen AC, Palmer DH, Morris K, Duggan M, Cunningham D, Anthoney DA, Corrie P, Madhusudan S, Maraveyas A, Ross PJ, Waters JS, Steward WP, Rees C, Beare S, Dive C, Bridgewater JA. Cediranib or placebo in combination with cisplatin and gemcitabine chemotherapy for patients with advanced biliary tract cancer (ABC-03): a randomised phase 2 trial. *Lancet Oncol* 2015; 16: 967-978 [PMID: 26179201 DOI: 10.1016/S1470-2045(15)00139-4]
57 Bengala C, Bertolini F, Malavasi N, Boni C, Aitini E, Dealis C, Zironi S, Depenni R, Fontana A, Del Giovane C, Luppi G, Conte P. Sorafenib in patients with advanced biliary tract carcinoma: a phase II trial. *Br J Cancer* 2010; 102: 68-72 [PMID: 19935794 DOI: 10.1038/sj.bjc.6605458]
58 El-Khoueiry A. A phase II study of sorafenib (BAY 43-9006) as single agent in patients (pts) with unresectable or metastatic gallbladder cancer or cholangiocarcinomas. *J Clin Oncol* 2007; 25
59 El-Khoueiry AB, Rankin C, Siegel AB, Iqbal S, Gong IY, Micetich KC, Kayaleh OR, Lenz HJ, Blanke CD. S0941: a phase 2 SWOG study of sorafenib and erlotinib in patients with advanced gallbladder carcinoma or cholangiocarcinoma. *Br J Cancer* 2014; 110: 882-887 [PMID: 24423918 DOI: 10.1038/bjc.2013.801]
60 Lee JK, Capanu M, O'Reilly EM, Ma J, Chou JF, Shia J, Katz SS, Gansukh B, Reidy-Lagunes D, Segal NH, Yu KH, Chung KY, Saltz LB, Abou-Alfa GK. A phase II study of gemcitabine and cisplatin plus sorafenib in patients with advanced biliary adenocarcinomas. *Br J Cancer* 2013; 109: 915-919 [PMID: 23900219 DOI: 10.1038/bjc.2013.432]
61 Moehler M, Maderer A, Schimanski C, Kanzler S, Denzer U, Kolligs FT, Ebert MP, Distelrath A, Geissler M, Trojan J, Schütz M, Berie L, Sauvigny C, Lammert F, Lohse A, Dollinger MM, Lindig U, Duerr EM, Lubomierski N, Zimmermann S, Wachtlin D, Kaiser AK, Schadmand-Fischer S, Galle PR, Woerns M; Working Group of Internal Oncology. Gemcitabine plus sorafenib versus gemcitabine alone in advanced biliary tract cancer: a double-blind placebo-controlled multicentre phase II AIO study with biomarker and serum programme. *Eur J Cancer* 2014; 50: 3125-3135 [PMID: 25446376 DOI: 10.1016/j.ejca.2014.09.013]
62 Yi JH, Thongprasert S, Lee J, Doval DC, Park SH, Park JO, Park YS, Kang WK, Lim HY. A phase II study of sunitinib as a second-line treatment in advanced biliary tract carcinoma: a multicentre, multinational study. *Eur J Cancer* 2012; 48: 196-201 [PMID: 22176869 DOI: 10.1016/j.ejca.2011.11.017]
63 Santoro A, Gebbia V, Pressiani T, Testa A, Personeni N, Arrivas Bajardi E, Foa P, Buonadonna A, Bencardino K, Barone C, Ferrari D, Zaniboni A, Tronconi MC, Cartenì G, Milella M, Comandone A, Ferrari S, Rimassa L. A randomized, multicenter, phase II study of vandetanib monotherapy versus vandetanib in combination with gemcitabine versus gemcitabine plus placebo in subjects with advanced biliary tract cancer: the VanGogh study. *Ann Oncol* 2015; 26: 542-547 [PMID: 25538178 DOI: 10.1093/annonc/mdu576]
64 Kawamata F, Kamachi H, Einama T, Homma S, Tahara M, Miyazaki M, Tanaka S, Kamiyama T, Nishihara H, Taketomi A, Todo S. Intracellular localization of mesothelin predicts patient prognosis of extrahepatic bile duct cancer. *Int J Oncol* 2012; 41: 2109-2118 [PMID: 23064529 DOI: 10.3892/

ijo.2012.1662]
65 Nomura R, Fujii H, Abe M, Sugo H, Ishizaki Y, Kawasaki S, Hino O. Mesothelin expression is a prognostic factor in cholangiocellular carcinoma. *Int Surg* 2013; 98: 164-169 [PMID: 23701154 DOI: 10.9738/INTSURG-D-13-00001.1]
66 Ross JS, Wang K, Gay L, Al-Rohil R, Rand JV, Jones DM, Lee HJ, Sheehan CE, Otto GA, Palmer G, Yelensky R, Lipson D, Morosini D, Hawryluk M, Catenacci DV, Miller VA, Churi C, Ali S, Stephens PJ. New routes to targeted therapy of intrahepatic cholangiocarcinomas revealed by next-generation sequencing. *Oncologist* 2014; 19: 235-242 [PMID: 24563076 DOI: 10.1634/theoncologist.2013-0352]
67 Farshidfar F, Zheng S, Gingras MC, Newton Y, Shih J, Robertson AG, Hinoue T, Hoadley KA, Gibb EA, Roszik J, Covington KR, Wu CC, Shinbrot E, Stransky N, Hegde A, Yang JD, Reznik E, Sadeghi S, Pedamallu CS, Ojesina AI, Hess JM, Auman JT, Rhie SK, Bowlby R, Borad MJ; Cancer Genome Atlas Network, Zhu AX, Stuart JM, Sander C, Akbani R, Cherniack AD, Deshpande V, Mounajjed T, Foo WC, Torbenson MS, Kleiner DE, Laird PW, Wheeler DA, McRee AJ, Bathe OF, Andersen JB, Bardeesy N, Roberts LR, Kwong LN. Integrative Genomic Analysis of Cholangiocarcinoma Identifies Distinct IDH-Mutant Molecular Profiles. *Cell Rep* 2017; 18: 2780-2794 [PMID: 28297679 DOI: 10.1016/j.celrep.2017.02.033]
68 Churi CR, Shroff R, Wang Y, Rashid A, Kang HC, Weatherly J, Zuo M, Zinner R, Hong D, Meric-Bernstam F, Janku F, Crane CH, Mishra L, Vauthey JN, Wolff RA, Mills G, Javle M. Mutation profiling in cholangiocarcinoma: prognostic and therapeutic implications. *PLoS One* 2014; 9: e115383 [PMID: 25536104 DOI: 10.1371/journal.pone.0115383]
69 Golan T, Raitses-Gurevich M, Kelley RK, Bocobo AG, Borgida A, Shroff RT, Holter S, Gallinger S, Ahn DH, Aderka D, Apurva J, Bekaii-Saab T, Friedman E, Javle M. Overall Survival and Clinical Characteristics of BRCA-Associated Cholangiocarcinoma: A Multicenter Retrospective Study. *Oncologist* 2017; 22: 804-810 [PMID: 28487467 DOI: 10.1634/theoncologist.2016-0415]

编辑: 崔丽君 电编: 张砚梁

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

• 消息 •

《世界华人消化杂志》正文要求

本刊讯 本刊正文标题层次为 0引言; 1 材料和方法, 1.1 材料, 1.2 方法; 2 结果; 3 讨论; 4 参考文献. 序号一律左顶格写, 后空1格写标题; 2级标题后空1格接正文. 以下逐条陈述: (1)引言 应包括该研究的目的和该研究与其他相关研究的关系. (2)材料和方法 应尽量简短, 但应让其他有经验的研究者能够重复该实验. 对新的方法应该详细描述, 以前发表过的方法引用参考文献即可, 有关文献中或试剂手册中的方法的改进仅描述改进之处即可. (3)结果 实验结果应合理采用图表和文字表示, 在结果中应避免讨论. (4)讨论 要简明, 应集中对所得的结果做出解释而不是重复叙述, 也不应是大量文献的回顾. 图表的数量要精选. 表应有表序和表题, 并有足够具有自明性的信息, 使读者不查阅正文即可理解该表的内容. 表内每一栏均应有表头, 表内非公知通用缩写应在表注中说明, 表格一律使用三线表(不用竖线), 在正文中该出现的地方应注出. 图应有图序、图题和图注, 以使其容易被读者理解, 所有的图应在正文中该出现的地方注出. 同一个主题内容的彩色图、黑白图、线条图, 统一用一个注解分别叙述. 如: 图1 萎缩性胃炎治疗前后病理变化. A: …; B: …; C: …; D: …; E: …; F: …; G: …. 曲线图可按●、○、■、□、▲、△顺序使用标准的符号. 统计学显著性用: $^{a}P<0.05$, $^{b}P<0.01$($P>0.05$不注). 如同一表中另有一套P值, 则$^{c}P<0.05$, $^{d}P<0.01$; 第3套为$^{e}P<0.05$, $^{f}P<0.01$. P值后注明何种检验及其具体数字, 如$P<0.01$, $t = 4.56$ *vs* 对照组等, 注在表的左下方. 表内采用阿拉伯数字, 共同的计量单位符号应注在表的右上方, 表内个位数、小数点、±、-应上下对齐. “空白”表示无此项或未测, “-”代表阴性未发现, 不能用同左、同上等. 表图勿与正文内容重复. 表图的标目尽量用t/min, c/(mol/L), p/kPa, V/mL, t/℃表达. 黑白图请附黑白照片, 并拷入光盘内; 彩色图请提供冲洗的彩色照片, 请不要提供计算机打印的照片. 彩色图片大小7.5 cm ×4.5 cm, 必须使用双面胶条黏贴在正文内, 不能使用浆糊黏贴. (5)志谢 后加冒号, 排在讨论后及参考文献前, 左齐.

Baishideng®

Published by **Baishideng Publishing Group Inc**
7901 Stoneridge Drive, Suite 501, Pleasanton,
CA 94588, USA
Fax: +1-925-223-8242
Telephone: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
http://www.wjgnet.com

ISSN 1009-3079