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文献综述 REVIEW

潜在可切除结直肠癌肝转移转化治疗的研究进展

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Conversion therapy for colorectal cancer patients with potentially resectable liver metastases

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Abstract
Conversion therapy brings hope of a cure for colorectal cancer patients with potentially resectable liver metastases. Recent studies demonstrated that conversion therapy could achieve shrinkage of liver metastases and thus render some for resection and offer the chance of long-term survival. Besides preoperative systemic chemotherapy, oncosurgical modalities are also available, primarily including liver resection following portal vein ligation/embolization and two-stage liver resection. In this article, we will review recent advances in conversion therapy for these patients.

Key Words: Conversion therapy; Colorectal liver metastases; Potentially resectable

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摘要
转化治疗给潜在可切除的结直肠癌肝转移(colorectal liver metastases, CRLM)患者带来了治愈的希望. 近年, 一些研究表明转化治疗可以使肝转移灶出现缩小, 使部分初始不可切除的CRLM患者的转化为可切除, 从而使这部分患者获得长期生存. 在治疗的选择上, 除了全身化疗外, 门静脉栓塞/结扎、分期肝叶切除等一些外科手段也运用其中这使得更多初始不可切除的CRLM患者获得手术切除的机会. 本文将对转化治疗近期的发展近况作一介绍, 以供临床在诊治时可以作为参考.

关键词: 转化治疗; 结直肠癌肝转移; 潜在可切除

核心提示: 潜在可切除的结直肠癌肝转移患者是介于初始可切除与不可切除之间的患者, 以全身化疗及肝脏为导向的局部治疗是这部分患者获得手术切除及长期生存的关键.

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0 引言
肝脏是结直肠癌血行转移最主要的靶器官[1]. 肝转移灶无法切除患者的中位生存期仅6.9 mo, 5年生存率接近0%[2]; 而肝转移灶能根治性切除患者的中位生存期为35 mo, 5年生存率可达30%-50%[3]. 然而首次确诊时已经约有15%-25%的结直肠癌患者伴有肝转移, 其中只有10%-15%的患者适合手术切除, 绝大部分患者因肝外转移病变累及多支大血管和预留肝功能不足等因素而不能手术切除. 2012年《ESMO

■背景资料
大肠癌的发病率呈逐年上升的趋势, 而肝脏又是结直肠癌血行转移的主要靶器官. 手术切除肝转移灶是这部分患者获得长期生存的关键所在. 而转化治疗是初始不可切除的结直肠癌肝转移患者获得长期生存的希望.

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■研发前沿
新型分子标志物的发现带动了新型靶向药物的问世, 使得对肿瘤的治疗更有针对性, 朝着以个体为导向的方向发展.

结直肠癌诊疗共识指南》围绕转移灶是否能够切除和通过转化治疗进行转化把直肠癌肝(肺)转移患者分成了4组, 其中第1组是指肝和(或)肺转移灶初始难以达到R0切除, 但经过化疗或联合靶向等治疗可能R0切除, 即潜在可切除或初始不可切除的患者. 据报道, 潜在可切除的结直肠癌肝转移(colorectal liver metastases, CRLM)患者降期后的可切除率为13%-54%[4,5]. 转化治疗如何提高这组患者的手术切除率成为了一个热门话题.

转化治疗是指潜在可切除的CRLM患者, 通过某些治疗措施能使初始不可切除的病灶转化为可切除的方式. Bismuth等于1996年首次报道了对330例初始不可切除的CRLM患者进行术前化疗, 患者接受FOLFOX方案的术前化疗后53例(16%)患者转化为可切除, 5年生存率达到了40%, 这项研究成为了当代转化治疗的基石. 通常所说的转化治疗是以转化化疗为代表, 以缩小转移灶并将其转化为可切除的病灶的治疗方式; 对CRLM患者而言广义上的转化治疗实际上是多学科参与的以缩小肿瘤病灶和增加残肝体积为目的的一系列治疗, 包括化疗(联合靶向药物)、肝动脉灌注化疗(hepatic arterial infusion, HAI)、门静脉栓塞/结扎(porta vein embolization/ligation, PVE/L)、分期肝叶切除(two-stage hepatectomy, TSH). 通过上述方式的治疗可以使部分初始不可切除的CRLM患者出现肿瘤的退缩、残肝容积的增加从而使这部分患者获得手术切除的机会.

1 缩小(毁损)肿瘤的治疗

1.1 *转化化疗* 潜在可切除的CRLM患者推荐术前可采用短期多药联合、足量密集型的化疗方案, 也可联合分子靶向药物. 关于化疗时间, 推荐手术前至少进行2-3周期. 高强度的化疗能够提高初始不可切除的肝转移瘤转化的R0切除率, 为患者创造了手术机会. 强烈的化疗方案表现在药物种类的叠加上及药物剂量的增加.

1.1.1 *两药方案*: 5-氟尿嘧啶(5-fluorouracil, 5-FU)/亚叶酸钙(leucovorin calcium, LV)联合奥沙利铂(oxaliplatin, OXA)的化疗方案可使不可切除的CRLM患者获得7%-51%左右的肝切除率; 而联合伊立替康(irinotecan, CPT-11)的化疗方案可获得9%-35%左右的肝切除率[6]. Alberts等[7]对44例仅有肝转移CRLM患者给予FOLFOX4方案(5-FU、LV、O)的转化治疗, 反应率(response rate, RR)为60%, R0切除为40%. Pozzo等[8]使用FOLFIRI方案[5-FU(F)、亚叶酸钙(LV)、伊利替康(I)]对40例不可切除的患进行转化化疗, 客观反应率(objective response rate, ORR)为47.5%, 最终30%的患者转化为可切除. 这项研究2007年的随访结果显示[9], 两组患者的中位肿瘤进展时间分别为(14.3 mo *vs* 5.2 mo), 手术组的中位术后无病生存期为52.5 mo. 近年有关于增加伊立替康剂量以提高CRLM患者R0切除率的报道, 尿苷二磷酸葡糖醛酸转移酶1A1(uridine diphosphate glucuronosyl transferase 1A1, *UGT1A1*)基因状态被认为是指导伊利替康使用的分子标志物. 西班牙[10]的爬坡实验证明UGT1A1野生型的患者适合高剂量或标准剂量的伊立替康(450 mg/m^2), 杂合型患者适合的剂量为390 mg/m^2, 纯合子型的患者则推荐低剂量的伊立替康(150 mg/m^2). 卡培他滨、S-1作为5-FU类口服药物, 也已被多项研究证明可以安全替代5-FU/LV静滴与奥沙利铂、伊利替康联用, 不缩短PFS和OS[11-13].

1.1.2 *三药方案*: 两药联合方案取得显著疗效的同时使得研究者们开始关注三种细胞毒药物联合方案在CRLM患者中的使用. Falcone等[14]分析了既往7个随机三期临床研究结果, 发现那些在整个治疗过程中接受3种高效药物治疗的患者获得了更大的生存获益. 受此启发纳入了244例初始不可切除的CRLM患者, 随机分为FOLFOXIRI组[5-氟尿嘧啶(F)、亚叶酸钙(LV)、伊利替康(I)、奥沙利铂(O)]与FOLFIRI组, 结果显示三药联合方案可显著地提高仅肝转移患者的手术R0切除率(36% *vs* 12%), 无病生存率(9.8 mo *vs* 5.9 mo), 总生存率(22.6 mo *vs* 16.7 mo). 该研究随访结果显示R0切除的患者中29%的患者5年内未出现复发, 5年及8年的生存率分别达到了42%及33%[15]. 另一项随机对照的METHEP研究[16]比较了标准的二药化疗方案(FOLFIRI, high dose-FOLFIRI, FOLFOX-4, FOLFOX-7)和三药化疗方案(FOLFIRINOX)对不可切除CRLM患者的影响, 初步分析显示FOLFIRINOX方案和high dose-FOLFIRI方案组分别获得了52%和50%的客观缓解率, 而R0切除率分别达到了36%和37%, 同时两个高效化疗方案的安全性也是被肯定的.

1.2 *化疗联合靶向的治疗* 靶向药物(targeted medicine)通过与癌症发生、肿瘤生长所必需的特定分子靶点的作用来阻止癌细胞的生长.

近年分子靶向药物人血管内皮生长因子受体(vascular endothelial growth factor, VEGF)、表皮生长因子受体(epidermal growth factor receptor, EGFR)联合奥沙利铂/依立替康为主的化疗方案被运用于CRLM患者的术前治疗中被证明可以进一步提高转化率, 使得更多初始不可切除的CRLM患者行手术切除的机会.

(1)VEGF单抗: 贝伐珠单抗(bevacizumab)是针对VEGF的人源化单克隆抗体. 2003年美国Duke大学Herbert Hurwitz等报告了贝伐珠单抗治疗晚期大肠癌疗效显著, 引起高度关注. 关于贝伐单抗在治疗mCRC中的价值时各项研究有不同的意见. 在与铂类药物联合运用方面, In NO16966[17]研究结果示, 贝伐珠单抗与CapeOX[卡培他滨、OXA]/FOLFOX方案的联合一线治疗显著提高了患者的PFS(9.4 mo *vs* 8.0 mo, P = 0.0023), 但是在OS和RR上贝伐珠单抗与CapeOX/FOLFOX组与安慰剂组相比并无获益. 在与伊立替康联合方面AVF2107g[18]和ARTIST研究[19](静脉注射氟尿嘧啶联合伊利替康的IFL/mIFL方案)均证明了化疗联合贝伐单抗可使ORR提高10%并显著延长了患者的PFS与OS. BICC研究[20]是在优化伊利替康用法的同时, 比较FOLFIRI/BVZ方案与mIFL/BVZ方案用于一线治疗晚期肠癌患者, 结果示在中位OS上FOLFIRI/BVZ方案(28 mo *vs* 19.2 mo, P = 0.037)有获益, 而PFS、ORR上两组无显著差别. 贝伐珠单抗与FOLFOXIRI方案联合, 入组患者的疾病控制率达到了100%及76%的客观缓解率, 并使17%的患者获得了二次手术的机会, 并且不良反应是可控制的.

(2)EGFR单抗: 西妥昔单抗(cetuximab)是一种重组的人鼠嵌合性EGFR的单克隆抗体而大肠癌以及许多实体瘤中EGFR过度表达, 近年多篇报告显示其疗效与*KRAS*基因状态密切相关. 西妥昔单抗与伊利替康的联合的方案主要有CRYSTAL(一线联合FOLFORI), 与奥沙利铂的联合的方案主要有OPUS研究. CRYSTAL[21] Ⅲ期随机对照临床研究显示, 西妥昔单抗单抗联合FOLFIRI组及FOLFIRI组的无进展生存期的危险比为0.85(P = 0.048), ORR之比为1.4(P = 0.004). 对肿瘤组织标本KRAS突变状态与临床疗效的相关性显示, 野生型患者接受西妥昔单抗联合FOLFIRI治疗疗效明显优于单独FOLFIRI组. OPUS研究[22]是在FOLFOX4化疗的基础上联合西妥昔单抗一线治疗CRLM患者的与单纯FOLFOX4化疗组相比较, 结果显示对KRAS野生型mCRC患者, 与单独FOLFOX4化疗方案相比, 西妥昔单抗联合FOLFOX4化疗显著提高总缓解率(57.3% *vs* 34%, P = 0.0027), 肿瘤最佳缩小比例平均高11.6%, 显著延长PFS(8.3 mo *vs* 7.2 mo, P = 0.0064). CELIM研究[23]报道了FOLFOX6联合西妥昔单抗与FOLFORI联合西妥昔单抗一线治疗转移性CRLM患者, FOLFOX6联合西妥昔单抗组的RR为68%, R0切除率为20%; FOLFORI联合西妥昔单抗组的RR为57%, R0切除率为30%, 在所有入组的患者中70%的*KRAS*基因野生型患者肿瘤出现了退缩, 34%的*KRAS*基因野生型患者获得了R0切除. 然而, 在西妥昔单抗联合伊利替康或奥沙利铂为基础的传统两药化疗方案带来可喜结果的同时, 近期两项Ⅲ期随机对照研究质疑了西妥昔单抗联合奥沙利铂为基础方案的有效性. COIN研究[24,25]比较了奥沙利铂为基础的化疗(CapeOX/FOLFOX)联合或不联合西妥昔单抗治疗, 结果显示在*KRAS*基因野生型患者中(CapeOX/FOLFOX)联合西妥昔单抗与单纯化疗组OS、PFS上均无获益, *KRAS*基因野生型患者仅在RR上略有获益(59% *vs* 50%, P = 0.02). 2010年美国临床肿瘤学会(American Society of Clinical Oncology, ASCO)会议上对COIN研究的重新分组显示FOLFOX联合西妥昔单抗组在PFS上有获益(P = 0.07), 而CapeOX联合西妥昔单抗组无获益. 而NORDIC Ⅶ研究[26]将FLOX方案[5-FU(F)静脉推注, 亚叶酸钙(LV), 奥沙利铂(O)]作为化疗骨架. 患者随机分为3组: A组为FLOX治疗至进展, B组为FLOX+西妥昔单抗治疗至进展, C组为间断性FLOX(16 wk停药、疾病进展后恢复)+持续性西妥昔单抗治疗至进展. 主要终点指标是PFS. 结果示3组在PFS、RR、OS上均无显著差异. 303例KRAS野生型患者中, B组在PFS、OS、RR上与A组亦无显著差异.

*KRAS*基因状态被证明与西妥昔单抗疗效相关的同时, 对于西妥昔单抗联合奥沙利铂为基础的方案(OPUS、COIN、NORDIC Ⅶ)的研究进一步提示在与传统化疗联合的基础上如何合理有效地使用靶向药物给出一些证据. 故西妥昔单抗应该避免在奥沙利铂+卡培他滨或推注5-FU的基础上联合西妥昔单抗, 建议与FOLFIRI或FOLFOX方案联合使用美国国立综合癌症网络(National Comprehensive Cancer Network, NCCN)指南不推荐西妥昔单抗与FOLFOX方案

■相关报道
尽管多药联合、足量密集型的化疗方案, 或与靶向药物联合的治疗模式已被指南所推荐, 但其不良反应是制约其运用的主要因素.

■**创新盘点**
结直肠癌肝转移治疗手段多样化, 概念及指南更新频繁. 在已发表的文献中存在着选题范围过大导致对问题的阐述不充分. 本文选题范围小, 将这部分的研究成果逐一进行阐述, 相对而言对临床的指导价值更高.

联合使用. 另外*BRAF*基因状态被证实只是一个预后不良的标志而不是西妥昔单抗疗效的基因标志物[27].

(3)帕尼单抗(panitumumab): 帕尼单抗是一种完全人源化的单克隆抗体, 与EGFR具有高度亲和性, 可以同时阻断EGF和TGF-2α与EGFR结合, 且半衰期更长. PRIME研究[28]结果示在*KRAS*基因野生型患者中(93%), 帕尼单抗-FOLFOX4组较FOLFOX4组在PFS(9.6 mo *vs* 8.0 mo, $P = 0.02$)有优势, 而OS并无获益; *KRAS*基因野生型组较*KRAS*基因突变组PFS明显获益, 在RR上两组分别为55%、48%. 另一项随机III期临床研究[29]比较了帕尼单抗联合FOLFIRI组与FOLFIRI组二线治疗mCRC患者, 联合帕尼单抗后RR具有明显优势(35% *vs* 10%). GONO[30]报道了FOLFOXIRI方案联合帕尼单抗一线治疗(KRAS、NRAS、HRAS、BRAF)均野生型的mCRC患者的II期临床研究. 研究入组了37例mCRC患者, 33例(89%)达到了客观缓解, 16例行二期手术的患者中有13例(35%)获得了R0切除. 在随后的17.7 mo的随访中, mPFS 为11.3 mo.

(4)靶向药物的联合应用: 靶向药物联合应用在转移性大肠癌治疗中的作用已有文献报道, 但结果令人失望. CAIR02研究[31]对CapeOX联合贝伐单抗基础上能否进一步联合C225进行了探讨, PACCE研究[32]对L-OHP/CPT-11一线化疗联合贝伐珠单抗基础上能否进一步联合帕尼单抗进行了探讨, 发现靶向药物两两联合未能对疗效和远期生存产生影响, 甚至反而增加毒性.

1.3 *肝动脉灌注化疗* 由于肝转移癌血供90%-100%来自肝动脉, 经肝动脉灌注化疗肝动脉灌注化疗(hepatic arterial infusion, HAI)药物, 由于药物首先经过肝脏, 可以在病灶局部形成较高的药物浓度, 有利于提高化疗效果这成为HAI的理论基础. 去氧氟尿苷(doxifluridine, FUDR)在肝脏的首过提取率可达94%, 是较好的局部化疗药物. 对于初始不可切除的CRLM患者, 运用HAI可获得较高的客观反应率(55%-70%)和R0切除率(16%-18%)[33,34]. 一项Meta研究[35]分析了近期10项随机对照研究, 比较以氟尿嘧啶为基础的HAI组与全身化疗组对初始不可切除的CRLM患者的影响, 结果HAI组较化疗组在肿瘤客观反映率上有明显优势(42.9% *vs* 18.4%, $P<0.0001$), 但在OS上并无获益. 提示HAI对肿瘤的退缩或许是一种较佳的治疗方式. 目前并无高级别的研究表明HAI可以代替全身化疗作为一种主要的转化治疗方式, 虽然HAI被证明有效, 但是HAI并不比全身化疗具有显著优势, 只是建议与全身化疗联合使用可能有助于延长患者的OS.

1.4 *转化化疗的问题* 术前短期多药联合、足量密集型的强烈的化疗方案虽然带来了R0切除率的提高, 明显增加了CRLM患者的生存获益, 但随之而来的肝损伤也开始被高度关注. 奥沙利铂为主的化疗可导致肝窦间隙扩张; 伊立替康为主的化疗可导致脂肪性肝炎. 这些肝损害这种损伤可能导致手术风险增加, 甚至导致转移灶无法切除增加术后并发症的发生率[36,37]. 贝伐珠单抗可增加器官穿孔、出血的风险, 并且抑制伤口愈合; 同时由于血管内皮生长因子在肝脏再生中发挥重要作用, 因此术前接受血管内皮生长因子拮抗剂可能致术后肝脏再生能力下降, 增加术后肝衰竭的风险[38,39], 因此建议停用贝伐珠单抗后6 wk(2个贝伐单抗半衰期)进行手术治疗. 为减轻化疗性肝损伤的发生术前化疗时间不宜超过3-4 mo. 对经过转化治疗有望达到R0切除的患者, 由于放射学方法证实的化疗后完全缓解(complete clinical response, CCR)约有83%的灶经病理学检查或随访发现仍有活的癌细胞, 建议在影像学病灶消失前进行切除, 避免CCR的发生[40].

2 增大正常肝体积的治疗

增大肝脏体积的治疗主要是为了解决因手术切除肝脏转移灶后面临的残肝体积不足而无法手术的难点. 这部分患者需要或并不需要术前化疗使转移灶出现退缩, 重要的是手术后要有足够肝脏组织能满足基本生理功能的需求. 肝脏细胞属于暂不增值细胞当遭遇手术等打击后可再次进入细胞周期这为增大残肝体积的方法提供了一定的理论基础, 增大肝脏体积的治疗主要包括以下两种方法.

2.1 PVE/L 当进行右半肝三区肝切除或右半肝切除术后左半肝体积过小, 此时虽然两个相邻的肝段存在充分的血液循环和胆汁引流, 但剩余的肝实质不能代偿而发生肝衰竭. 为了避免手术后因残肝体积过小需要一种方法使得肝脏体积增大而适合手术的切除. Kinoshita等[41]与Makuuchi等[42]发现肝癌或胆管癌的患者肿瘤侵犯门静脉右支后受阻塞部分的肝叶发生了萎缩而对侧肝脏即出现代偿性肥大. 受此启发门静脉栓塞术被用于切除肝脏的体积过大或者预计

保留的正常肝脏体积不足总体积的30%的病例[43,44]. PVE/L后, 通过3-9 wk的肝脏再生, 对侧肝脏增加的体积可以达到肝脏总体积的15%[45]. PVE/PVL术后可切除率约在60%-88%, 导致无法手术主要原因是行PVE/PVL术后肿瘤的进展[46]. 术后患者的5年生存率达到了38%左右. 一项Meta分析[47]显示PVE主要并发症是肝血肿、肝脓肿、左门静脉血栓形成、门脉高压、胆管炎, 发生率为2.2%, 死亡率为0.

2.2 TSH 当肝脏的左右两个肝叶都存在转移病灶时, PVE/PVL术在此时也是不适用的, 这类患者即使经手术切除肝转移病灶后也会因残肝体积不足而发生肝衰竭. 因此有学者引入了分期肝叶切除这个概念[48], 这个方法主要用于需要行右半肝或右肝三区切除, 同时左半肝或左肝外叶有转移灶的病例. TSH是一种整体的治疗方式, 这个治疗被分为两部分实施. 第1步, 先行原发肿瘤的根治性切除和残肝转移灶的局部切除, 一般位于左半肝或者左外叶, 并可同时行病侧PVE/L; 第2步, 行残留转移灶所分布的右半肝或右三肝切除. 二次肝切除前残肝体积的大小是决定是否能行二次肝切除的关键如果残肝体积过小, 此时PVE/L可以使残肝体积代偿的增大使得手术顺利进行. 另外为了避免肿瘤在两步之间的间隙发生进展, 有必要运用全身性的化疗或以肝脏局部化的治疗减小肝脏转移灶的体积. 同时为了避免化疗药物可能对再生肝组织的再生所产生的影响, 化疗应该在第一次肝切除后的3 wk开始以保证肝组织的再生的安全[49]. TSH分流了同时切除肿瘤组织和正常肝组织后的风险; 也评估了肿瘤对化疗的敏感性指导辅助化疗用药[50]. 近期一项回顾性研究[51]分析了459例接受TSH治疗的CRLM患者, 其总88%的患者首次肝脏手术前接受了转化化疗, 第一阶段肝切除后17%的患者接受了辅助化疗, 76%的患者也进行了PVE术. 最后有75%的患者获得了R0切除, 中位OS达到了37 mo. 所以针对其中的肝脏左右两个肝叶都存在转移病灶的患者而言分期肝叶切除是一种安全有效的转化治疗方式.

3 结论

转化治疗的发展无疑给潜在可切除的CRLM患者带来了巨大的生存获益. 虽然手术是CRLM患者最为理想的治疗方式但初始可获得手术治疗的患者比例低, 这成为了影响CRLM患者整体生存率的主要因素. 而转化治疗的发展, 从联合化疗到化疗联合靶向进一步提高了手术的R0切除率; 以增大残肝体积的治疗方式解决了因肝容量不足而导致的手术禁忌, 以上两方面又相互影响着治疗的整个过程, 使得临床工作中可以根据具体患者的情况制定出最佳的治疗决策争取获得手术切除的可能性. 同时转化治疗所带来的负面影响以及术后复发的也是不容忽视的. 转化治疗如何更好地运用于潜在可切除的CRLM患者这需要更多循证医学的证据的支持.

■应用要点

化疗联合靶向药物的治疗已被证实较联合化疗带来更高的R0切除率; 而对*KRAS*基因野生型的患者而言西妥昔单抗为主的方案较贝发单抗为主的方案有更高的转化切除率.

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■名词解释
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■同行评价

本文通过阐述转化治疗给潜在可切除的结直肠癌肝转移应用, 把近几年的研究成果逐一阐述. 内容客观、新颖, 对临床工作有一定的参考价值.

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• 消息 •

《世界华人消化杂志》外文字符标准

本刊讯 本刊论文出现的外文字符应注意大小写、正斜体与上下角标. 静脉注射iv, 肌肉注射im, 腹腔注射ip, 皮下注射sc, 脑室注射icv, 动脉注射ia, 口服*po*, 灌胃ig. s(秒)不能写成S, kg不能写成Kg, mL不能写成ML, $\frac{1}{2}$cpm(应写为1/min)÷E%(仪器效率)÷60 = Bq, pH不能写PH或P^H, *H pylori*不能写成HP, T1/2不能写成tl/2或T, *V*max不能Vmax, μ不写为英文u. 需排斜体的外文字, 用斜体表示. 如生物学中拉丁学名的属名与种名, 包括亚属、亚种、变种. 如幽门螺杆菌(*Helicobacter pylori*, *H.pylori*), *Ilex pubescens* Hook, *et* Arn.*var.glaber* Chang(命名者勿划横线); 常数*K*; 一些统计学符号(如样本数*n*, 均数mean, 标准差SD, *F*检验, *t*检验和概率*P*, 相关系数*r*); 化学名中标明取代位的元素、旋光性和构型符号(如*N*, *O*, *P*, *S*, *d*, *l*)如*n*-(normal, 正), *N*-(nitrogen, 氮), *o*-(ortho, 邻), *O*-(oxygen, 氧, 习惯不译), *d*-(dextro, 右旋), *p*-(para, 对), 例如*n*-butyl acetate(醋酸正丁酯), *N*-methylacetanilide(N-甲基乙酰苯胺), *o*-cresol(邻甲酚), 3-*O*-methyl-adrenaline(3-O-甲基肾上腺素), *d*-amphetamine(右旋苯丙胺), *l*-dopa(左旋多巴), *p*-aminosalicylic acid(对氨基水杨酸). 拉丁字及缩写*in vitro*, *in vivo*, *in situ*; Ibid, *et al*, *po*, *vs*; 用外文字母代表的物理量, 如*m*(质量), *V*(体积), *F*(力), *p*(压力), *W*(功), *v*(速度), *Q*(热量), *E*(电场强度), S(面积), *t*(时间), *z*(酶活性, kat), *t*(摄氏温度, ℃), *D*(吸收剂量, Gy), *A*(放射性活度, Bq), ρ(密度, 体积质量, g/L), *c*(浓度, mol/L), φ(体积分数, mL/L), *w*(质量分数, mg/g), *b*(质量摩尔浓度, mol/g), *l*(长度), *b*(宽度), *h*(高度), *d*(厚度), *R*(半径), *D*(直径), T_{max}, C_{max}, *V*d, $T_{1/2}$ *Cl*等. 基因符号通常用小写斜体, 如*ras*, *c-myc*; 基因产物用大写正体, 如P16蛋白.