Advances in Clinical Medicine 临床医学进展, 2023, 13(4), 6544-6549
Published Online April 2023 in Hans. https://www.hanspub.org/journal/acm
https://doi.org/10.12677/acm.2023.134917

Hans汉斯

雷替曲塞在消化系统肿瘤中的应用

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收稿日期：2023年3月24日；录用日期：2023年4月18日；发布日期：2023年4月26日

摘　要

消化系统肿瘤是临床上常见的恶性肿瘤。由于其起病隐匿、进展快，部分患者发现时已经错失手术机会，主要治疗方式为化疗为主的支持治疗。主要化疗药物为5-氟尿嘧啶，但由于5-氟尿嘧啶不良反应多、耐药产生等特点，我们急需探索新型药物改善目前状况。雷替曲塞作为一种新型化疗药物，因其抗肿瘤效果较好，不良反应小而脱颖而出，目前已作为氟尿嘧啶的替代药物广泛应用于治疗不适合5-氟尿嘧啶或亚叶酸钙的晚期结直肠癌患者。近年来，关于雷替曲塞对其他消化系统恶性肿瘤效益的研究也风靡云涌。如何让更多患者在雷替曲塞的治疗中获益，需要明确雷替曲塞是如何发挥抗肿瘤作用的，以及主要运用的领域。本文将讨论雷替曲塞发挥抗肿瘤的机制及其临床应用领域和不良反应，以更好地指导临床实践。

关键词

雷替曲塞，消化系统肿瘤，治疗，不良反应

Efficacy of Raltitrexed in Digestive System Tumors

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Received: Mar. 24th, 2023; accepted: Apr. 18th, 2023; published: Apr. 26th, 2023

Abstract

Digestive system tumors are a common clinical malignancy. Due to their insidious onset and rapid progress, some patients have missed the opportunity of surgery when found, and the main treatment method is chemotherapy-based supportive therapy. Main chemotherapy drug is 5-

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文章引用: 涂欣鑫, 李钺. 雷替曲塞在消化系统肿瘤中的应用[J]. 临床医学进展, 2023, 13(4): 6544-6549.
DOI: 10.12677/acm.2023.134917

fluorouracil, but due to its adverse reaction and drug resistance, we urgently need to explore new drugs to improve the current situation. As a new chemotherapeutic drug, realtitrexed stands out because of its good antitumor effect and small adverse effects and it has now been widely used as an alternative to fluorouracil in the treatment of advanced colorectal cancer patients who are not suitable for 5-fluorouracil or leucovorin calcium. In recent years, studies on the benefits of raltitrexed in other digestive malignancies have also become popular. How to enable more patients to benefit from the treatment of raltitrexed needs us to study how raltitrexed plays its antitumor role and the main areas of application. This summarize will discuss the mechanisms by which raltitrexed exerts antitumor and its clinical applications and adverse effects to better guide clinical practice.

Keywords

Raltitrexed, Digestive System Tumors, Treatment, Adverse Effects

1. 引言

消化系统肿瘤是临床的常见恶性肿瘤，然而因其发病隐匿，大部分患者就诊时肿瘤已发展至晚期，错过了最佳的手术时间。全身化疗则成为救治晚期肿瘤患者的重要手段。主要方案是以 5-氟尿嘧啶(5-Fu)为基础的进行全身化疗[1]，但其效率较低，耐药性较高[2]，且有较高的毒性，尤其是较高的心脏毒性[3]，限制了其临床应用。

雷替曲塞，也称为 ZD1694 或 Tomudex。其化学名称：N-[5-[N-甲基-N-(2-甲基-4-氧代-3，4-二氢喹唑啉-6-基甲基)氨基]-2-噻吩甲酰基]-L-谷氨酸。雷替曲塞作为一种新型化疗药物，因其抗肿瘤效果较好，不良反应小而脱颖而出，目前已广泛应用于治疗不适合 5-氟尿嘧啶或亚叶酸钙的晚期结直肠癌患者[4]。近年来，关于雷替曲塞对其他消化道肿瘤效益的研究也风靡云涌。本文对雷替曲塞对消化道肿瘤的应用进展进行综述，以更好地指导临床实践。

2. 介绍

2.1. 抗肿瘤微环境

雷替曲塞是一种特异性胸苷酸合酶(TS)抑制剂[5]，可通过阻断 G0/G1 期的细胞周期和通过线粒体途径诱导肿瘤细胞凋亡来减少肿瘤细胞的增殖[6]。研究表明，雷曲塞对结直肠癌、恶性间皮瘤、头颈癌、肝癌和胃癌均有抗癌活性[7]。首先，雷替曲塞上调了 HGC-4 (胃癌细胞系)细胞中的 RSK27 mRNA 和蛋白质水平[8]，此外，雷替曲塞可显著抑制肿瘤细胞集落形成，并阻止细胞周期进程，降低线粒体膜电位等途径来诱导细胞凋亡[8]。RSK4 作为核糖体蛋白 S6 激酶(RSK)家族，可显著抑制结肠癌、乳腺癌和胃癌的细胞增殖、迁移和侵袭，被认为是评估患者预后的标志物[9] [10]。Hu 等的研究表明 siRNA 介导的 RSK4 敲低显着降低了雷替曲塞对细胞增殖及其促进细胞凋亡的抑制作用[8]。此外，RSK4 表达的降低显著增加了肿瘤细胞集落形成，促进了细胞周期进程，并抑制了细胞凋亡。雷替曲塞显著降低了 HGC-27 细胞的线粒体膜电位，沉默 RSK4 可抑制雷替曲塞诱导的细胞色素 C 上调，表明雷替曲塞诱导的细胞凋亡通过线粒体途径介导[8]。而且，在 RSK4 耗竭时，与雷替曲塞诱导的细胞周期和细胞凋亡相关的分子

标志物的变化减少[8]。另有文献报道，阿帕替尼与雷替曲塞联合治疗对细胞增殖、迁移和侵袭性的抑制作用增强，下调了抗凋亡蛋白 Bcl-2 的 mRNA 水平，同时上调了促凋亡蛋白 PARP、Bax 基因和 Caspase-3 (半胱天冬酶-3)转录[11]。

雷替曲塞是高选择性抗代谢的细胞毒性药物，通过特异性地抑制，实现抑制肿瘤细胞的复制，达到抗肿瘤的效果。重要的是，其相较于氟尿嘧啶类药物的心脏毒性而言，雷替曲塞具有更小的心脏毒性[12] [13] [14]，可作为 5-FU 的替代性化疗药物[15]。雷替曲塞对氟尿嘧啶也有协同作用，可以抑制氟尿嘧啶靶酶的活性[16]。叶等研究表明，当二氢嘧啶脱氢酶(DPD)和 TS 的上调时，5-FU 对于结直肠癌效果较差，产生耐药，而 S-1 (DPD 抑制剂)联合雷替曲塞治疗难治性转移性结直肠癌疗效较好，可作为三线药物选择[17]。除此之外，雷替曲塞在 MYCN 基因扩张的神经母细胞瘤中也诱导高水平的 DNA 损伤，但目前对此方面研究较少[18]。

2.2. 灌注化疗

雷替曲塞常与其他药物用于经肝动脉化疗栓塞术(TACE)。研究表明，对于不可切除肝细胞癌，雷替曲塞联合奥沙利铂持续动脉灌注可有效地改善患者预后[4] [19] [20]。结直肠腹膜癌预后不良，腹膜是其最常见的转移部位之一，目前主要以肿瘤减灭手术手术辅以腹腔热化疗(HIPEC)治疗，但用于 HIPEC 的药物有限[21]。研究发现，重组突变人 TNF-α (rmhTNF)和雷替曲塞(RTX)与 42℃温度下的 HIPEC 进行组合在体外和体内均具有抗肿瘤作用[22]。在结直肠癌患者的临床治疗中，也同样观察到热灌注化疗对雷替曲塞具有协同作用，更有利于提高效益[23] [24]。对于结直肠癌肝转移患者，持续肝动脉微量泵入雷替曲塞可作为氟尿嘧啶的替代治疗，但二者之间在生存率和预后方面无统计学差异[25]。洗脱珠肝动脉化疗栓塞(DEB-TACE)在原发性肝癌的应用逐渐增多，加载表柔比星和雷曲塞的 DEB-TACE 可改善中晚期 PHC 患者的短期结局，减少肿瘤负荷，降低不良事件的发生率，并提高生存率[26]。

2.3. 纳米颗粒

一种透明质酸包被的纳米材料可通过逐层分装雷替曲塞，与放疗结合，输送至靶细胞，可更加精准有效的发挥抗肿瘤作用[27]。也有研究表明，负载雷替曲塞的纳米材料在结直肠癌的治疗中可更好地改善预后[28]。这种在纳米颗粒制剂中加载雷替曲塞的方法，建立了联合放疗和药物给药方案，对未来多学科联合治疗具有重要意义。然而，雷替曲塞修饰的纳米颗粒的作用与纳米材料的材质有关，研究表明，银纳米颗粒的抗肿瘤作用大于金纳米颗粒[29]。准确地选择纳米颗粒和药物装置能给肿瘤患者带来更好的治疗效果，但目前由于纳米材料及其药物制备等技术成本问题，临床应用较少。

2.4. 放射治疗

研究表明，雷替曲塞可以通过 G2/G0 阻滞抑制肿瘤细胞增殖，诱导癌细胞凋亡，同时也可增强辐射诱导的细胞凋亡和 G2/G0 阻滞[6]。雷替曲塞与放疗结合较多运用与鼻咽癌等解剖位置特殊的患者[7] [30] [31]。对于转移性结直肠癌，雷替曲塞也能很好地到达靶细胞发挥抗肿瘤作用。但是对于可切除的局部晚期结直肠癌，术前放化疗联合雷替曲塞并无明显提高病理缓解率，且增加毒副反应[32]。然而，Adnan 的研究发现局部晚期直肠癌术前放化疗同时推注雷替曲塞的不良反应较氟尿嘧啶更少，但两者在括约肌保留、病理完全缓解、局部控制和远处复发率方面无显著差异[33]。雷替曲塞在放疗中的作用目前还研究较少，根据肿瘤微创化、综合化的治疗理念，这方面的发展将更能有效的指导临床实践。

2.5. 不良反应

雷曲塞最常见的不良事件是中性粒细胞减少、腹泻和肝酶升高[34]。与 5-FU 相比，雷替曲塞具有更

好的血液学和胃肠道耐受性，并且由于它不会引起相关代谢物的积累，因此心脏毒性较低[16] [35]。与5FU加亚叶酸钙相比，雷替曲塞的重度白细胞减少和黏膜炎发生率较低[35]。尽管TS是雷替曲塞治疗的主要靶标，但仍有其他可能的靶点参与其肿瘤抑制活性。国内临床试验显示本品联合奥沙利铂的不良反应主要包括恶心、呕吐、乏力、腹泻、中性粒细胞减少、贫血，血小板减少、转氨酶升高等，试验组粒细胞减少的发生率高于对照组，但两组因粒细胞缺乏所致的剂量调整无明显差别，两组使用升白药物患者的比例相当，未发生与粒细胞减少相关的严重不良事件。转氨酶升高多为I/II度，无症状且可逆。与对照组相比III/IV度转氨酶升高的发生率两组间无明显差别。

雷替曲塞也有耐药的发生率，但较5-氟尿嘧啶低。曹等研究表明：雷替曲塞诱导了肿瘤细胞增殖抑制、诱导了肿瘤细胞凋亡和自噬，但是雷替曲塞诱导肿瘤细胞发生的自噬拮抗了其抗癌效应，这可能是雷替曲塞发生耐药的分子机制之一[36]。但通过选择性改变TS构象，可作为未来克服耐药性的方法之一[37]。

3. 总结与展望

雷替曲塞作为新型抗肿瘤药物逐渐在消化系统肿瘤的治疗上占据重要地位。随着对雷替曲塞抗肿瘤机制的研究的进展，雷替曲塞不仅在灌注化疗、放疗、包被纳米颗粒等领域的运用逐渐广泛，还具有心肌毒性小、不良反应少等临床特点。但是目前对雷替曲塞的作用机制及其他作用还尚未明确，仍需要大量的实验研究探索。明确雷替曲塞的抗肿瘤之际，开发其在恶性肿瘤中的应用，对改善恶性肿瘤患者的预后具有重要意义。

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附　录

【中英文缩略对照】

英文缩写	英文全称	中文全称
5-Fu	5-fluorouracil	5-氟尿嘧啶
Tomudex	Tomudex	雷替曲塞
TS	Thymidylate Synthase	胸苷酸合成酶
HGC-4	Human Gastric Cancer Cells-4	人胃癌细胞-4
RSK	Ribosomal Protein S6 Kinase	核糖体蛋白 S6 激酶
Bcl-2	B-cell lymphoma-2	B 淋巴细胞瘤-2 基因
PARP	poly-ADP-ribose polymerase	聚腺苷二磷酸－核糖聚合酶
Caspase-3	Caspase-3	半胱天冬酶-3
DPD	dihydropyrimidine dehydrogenase	二氢嘧啶脱氢酶
MYCN	MyelocytomaViral Oncogene Homolog Genes	骨髓细胞瘤病毒相关基因
TACE	Transhepatic Arterial Chemoembolization	经肝动脉化疗栓塞术
HIPEC	Hyperthermic Intraperitoneal Chemotherapy	腹腔内热化疗
rmhTNF	Recombinant Mutant Human TNF-α	重组突变人 TNF-α
PTX	Raltitrexed	雷替曲塞
DEB-TACE	Drug-eluting Bead Transarterial Chemoembolization	洗脱珠肝动脉化疗栓塞