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REVIEW

Raltitrexed in Hepatocellular Carcinoma: Mechanistic Rationale and Clinical Evidence from Arterial-Based Therapies

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Abstract: Hepatocellular carcinoma (HCC) is a leading cause of cancer-related mortality worldwide and is frequently diagnosed at an advanced stage, resulting in limited eligibility for curative therapies and suboptimal outcomes with systemic treatment alone. Locoregional arterial therapies, including transarterial chemoembolization (TACE) and hepatic arterial infusion chemotherapy (HAIC), therefore remain integral components of treatment for unresectable HCC. Raltitrexed is a quinazoline antifolate that directly and specifically inhibits thymidylate synthase, leading to sustained suppression of DNA synthesis. Compared with 5-fluorouracil, raltitrexed offers distinct pharmacokinetic and practical advantages, including prolonged intracellular retention and a short infusion schedule. Originally developed for colorectal cancer, raltitrexed has been increasingly incorporated into arterial-based treatment strategies for HCC over the past decade. Accumulating evidence from retrospective studies, prospective single-arm trials, and limited comparative analyses suggests that raltitrexed-based regimens demonstrate meaningful antitumor activity in conventional and drug-eluting bead TACE, as well as in oxaliplatin-based HAIC, with objective response rates, disease control, and survival outcomes comparable to established chemotherapy protocols. Notably, raltitrexed-based HAIC substantially reduces infusion time relative to fluorouracil-based regimens, improving treatment convenience without compromising efficacy. More recently, raltitrexed-containing HAIC has been explored in combination with targeted therapy and immune checkpoint inhibitors, yielding encouraging response rates and survival signals in patients with advanced disease. Overall, raltitrexed represents a rational and increasingly utilized component of arterial-based therapies for unresectable HCC. However, current evidence is predominantly derived from retrospective and single-arm studies, and well-designed randomized trials and biomarker-driven approaches are required to define its optimal role in clinical practice.

Keywords: hepatocellular carcinoma, raltitrexed, transarterial chemoembolization, hepatic arterial infusion chemotherapy, locoregional therapy

Introduction

Hepatocellular carcinoma (HCC) remains one of the leading causes of cancer-related mortality worldwide and is frequently diagnosed at an advanced stage, precluding curative treatment options such as surgical resection, liver transplantation, or local ablation.[1,2] Although the therapeutic landscape of advanced HCC has evolved substantially with the introduction of tyrosine kinase inhibitors (TKIs) and immune checkpoint inhibitors (ICIs), clinical outcomes remain unsatisfactory, particularly in patients with large tumor burden.[3] In this context, locoregional and regional arterial therapies continue to play a central role across multiple disease stages, either as stand-alone treatments or as part of combined therapeutic strategies.[4,5]

Transarterial chemoembolization (TACE) and hepatic arterial infusion chemotherapy (HAIC) take advantage of the unique vascular characteristics of HCC, which derives the majority of its blood supply from the hepatic artery.[6,7] This anatomical feature enables selective delivery of cytotoxic agents at high intratumoral concentrations while minimizing systemic exposure.[6] Despite their widespread clinical application, there is currently no consensus regarding the optimal chemotherapeutic agents or regimens for either TACE or HAIC.[4] Anthracyclines and fluoropyrimidines have historically

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been the most commonly used drugs; however, their clinical utility is limited by drug resistance, cumulative toxicity, and practical constraints, including the requirement for prolonged continuous infusion in the case of fluoropyrimidines.[8,9]

Raltitrexed, a direct and specific thymidylate synthase (TS) inhibitor originally developed for colorectal cancer, has attracted increasing interest in the treatment of HCC.[10] In contrast to fluoropyrimidines, raltitrexed provides sustained TS inhibition through intracellular polyglutamation and can be administered over a short infusion period, offering both pharmacological and logistical advantages.[11] Over the past decade, raltitrexed has been progressively incorporated into conventional TACE (cTACE), drug-eluting bead TACE (dTACE), and oxaliplatin-based HAIC regimens, either as monotherapy or in combination with systemic agents. This narrative review summarizes the mechanistic basis, pharmacokinetic properties, clinical efficacy, combination strategies, and safety profile of raltitrexed in HCC, with a particular focus on its application in arterial-based therapeutic approaches.

Mechanisms and Pharmacokinetics of Raltitrexed

Raltitrexed is a quinazoline antifolate that acts as a direct and highly specific inhibitor of thymidylate synthase, a key enzyme in the *de novo* synthesis of deoxythymidine monophosphate (dTMP), which is essential for DNA replication and repair.[11] TS catalyzes the conversion of deoxyuridine monophosphate (dUMP) to dTMP using 5,10-methylenetetrahydrofolate as a methyl donor.[12] Although TS is a common target of several cytotoxic agents, the mechanisms by which these agents inhibit TS differ substantially.[12]

Unlike fluoropyrimidines such as 5-fluorouracil (5-FU), which exert indirect TS inhibition through the formation of fluorodeoxyuridine monophosphate (FdUMP) that competes with dUMP at the substrate-binding site,[13] raltitrexed binds non-competitively to the folate cofactor-binding site of TS (Figure 1).[11] This interaction prevents cofactor binding and directly blocks dTMP synthesis. Importantly, raltitrexed is not incorporated into nucleic acids, and its inhibitory effect cannot be overcome by intracellular accumulation of dUMP. Preclinical studies have demonstrated that raltitrexed is more potent than 5-FU, either alone or modulated with leucovorin, with half-maximal inhibitory concentrations in the the 1–10 nmol/L range.[11]

A defining pharmacological feature of raltitrexed is its intracellular metabolic activation. Following cellular uptake via the reduced folate carrier (RFC), raltitrexed undergoes rapid polyglutamation by folylpolyglutamate synthetase

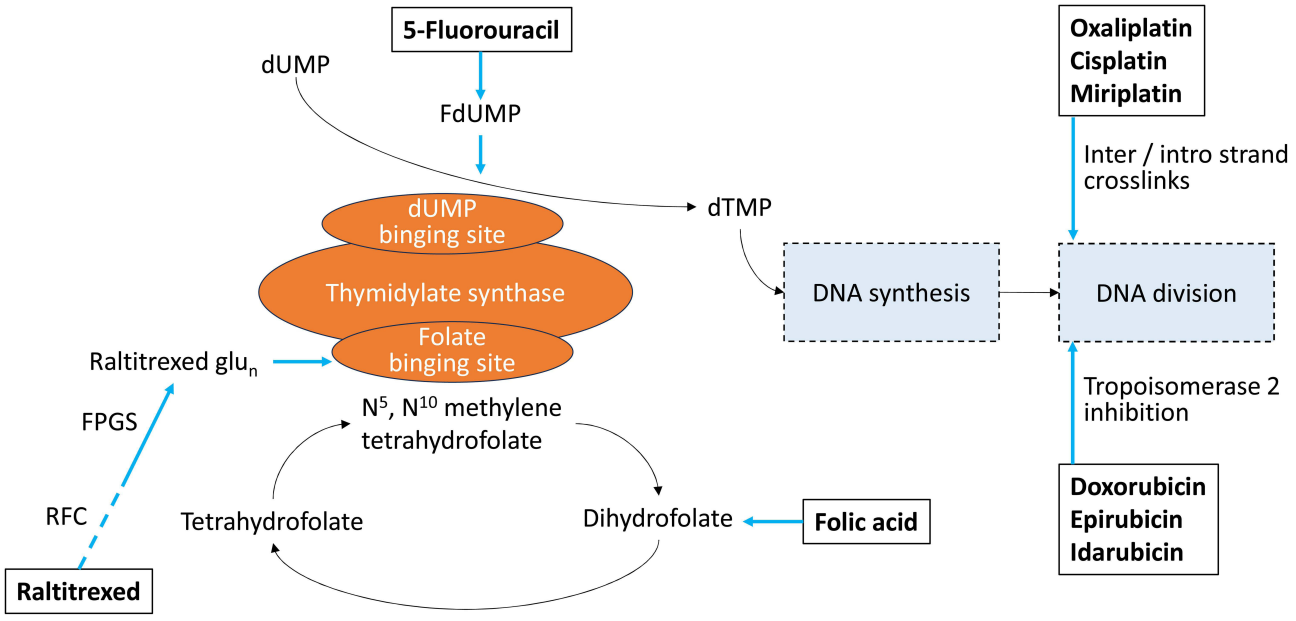

Figure 1 Mechanism of action of the common chemotherapy agents for hepatocellular carcinoma. 5-Fluorouracil is metabolized to FdUMP, which competitively inhibits thymidylate synthase, thereby blocking the conversion of deoxyuridine monophosphate (dUMP) to deoxythymidine monophosphate (dTMP). Leucovorin (folic acid) enhances this by increasing methylenetetrahydrofolate. Raltitrexed enters cells via the reduced folate carrier (RFC) and is polyglutamated by folylpolyglutamate synthetase (FPGS). The resulting polyglutamate form of raltitrexed non-competitively inhibits thymidylate synthase by binding to its folate cofactor site, suppressing dTMP synthesis.

(FPGS).[12] These polyglutamated metabolites exhibit enhanced affinity for TS and prolonged intracellular retention, resulting in sustained enzyme inhibition even after plasma clearance of the parent compound. Experimental models have shown tissue concentrations of polyglutamated raltitrexed that far exceed plasma levels several hours after administration.[14] In contrast to 5-FU, which has a very short plasma half-life, raltitrexed displays a triphasic elimination profile with a prolonged terminal half-life.[12] These pharmacokinetic characteristics allow administration as a short intravenous infusion, providing a strong rationale for its use in TACE and HAIC, where treatment efficiency, patient convenience, and catheter management are important considerations.

Systemic Therapy Using Raltitrexed Alone

The clinical activity of raltitrexed as monotherapy in HCC has been evaluated in a limited number of early-phase studies. In a Phase II trial of intravenous raltitrexed administered at 3.0 mg/m^2 every 21 days in patients with advanced HCC, no complete or partial responses were observed among 26 evaluable patients.[15] Stable disease was achieved in 46% of patients, while 54% experienced disease progression. Notably, minor tumor shrinkage and reductions in serum alpha-fetoprotein levels were observed in a subset of patients, indicating modest biological activity. Overall, these findings suggest that raltitrexed alone has limited antitumor efficacy in advanced HCC and does not support its further development as monotherapy. Consequently, subsequent investigations have focused on its use in locoregional settings or in combination with other therapeutic agents.

Raltitrexed in TACE

TACE remains a cornerstone locoregional therapy for patients with unresectable HCC, particularly those with intermediate-stage disease according to the Barcelona Clinic Liver Cancer staging system.[16,17] By selectively delivering chemotherapeutic agents into tumor-feeding arteries followed by embolization, TACE induces ischemic tumor necrosis while achieving high intratumoral drug concentrations and minimizing systemic exposure. Two principal modalities are currently used in clinical practice: cTACE and dTACE. While randomized controlled trials have demonstrated comparable survival outcomes between these approaches,[18–21] dTACE may offer advantages in selected patient populations and is generally associated with lower systemic toxicity.[22]

Raltitrexed in cTACE

The first randomized evidence supporting the use of raltitrexed in cTACE for HCC was provided by Zhao et al in a multicenter randomized controlled trial comparing raltitrexed-based TACE with fluorouracil- and doxorubicin-based regimens.[23] Patients treated with raltitrexed achieved a significantly longer median overall survival of 13.4 months, accompanied by improvements in progression-free survival (6.7 months) and objective response rate (65%), establishing raltitrexed as an active cytotoxic agent in the cTACE setting.

Subsequent prospective and real-world studies further supported these findings. In a prospective cohort study enrolling 123 patients with unresectable HCC, Shao et al reported a median overall survival of 20.8 months and a median progression-free survival of 11.3 months following raltitrexed-based cTACE, with an objective response rate of 43.1% and a disease control rate of 95.5%.[24] These outcomes compared favorably with historical results obtained using anthracycline- or fluorouracil-based regimens.

Evidence from real-world practice has also suggested a potential survival advantage of raltitrexed-based cTACE. In a multicenter propensity score–matched analysis, He et al demonstrated that patients treated with raltitrexed-based cTACE experienced significantly longer overall survival and higher disease control rates compared with those receiving non-raltitrexed regimens, supporting the clinical effectiveness of raltitrexed beyond controlled trial settings.[25]

Beyond efficacy, efforts have been made to identify biomarkers predictive of response to raltitrexed-based cTACE. In a case–control study, Qi et al investigated the association between thymidylate synthase (TYMS) gene polymorphisms and treatment outcomes.[26] Patients carrying the 3R/3R genotype exhibited higher objective response rates and longer progression-free survival compared with other genotypes, suggesting that interindividual variability in TS expression may influence sensitivity to raltitrexed. These findings highlight the potential for biomarker-driven patient selection in future studies.

Raltitrexed in dTACE

Raltitrexed has been explored as a payload for dTACE in several clinical studies. In a retrospective analysis of patients with unresectable or recurrent HCC treated with raltitrexed-loaded microspheres, high objective response rates were reported at the first radiological assessment, with disease control rates approaching 90%.[27] Importantly, prolonged overall survival and progression-free survival were observed in selected patients, suggesting durable tumor control.[27]

Comparative evidence has been provided by propensity score-matched analyses evaluating dTACE loaded with different chemotherapeutic agents, including raltitrexed and anthracyclines.[28] Although short-term objective response rates were numerically lower in the raltitrexed group, long-term survival outcomes were comparable across treatment arms, indicating that raltitrexed-eluting beads may achieve similar durable efficacy.[28]

More recently, a prospective single-arm study in patients with intermediate-stage HCC reported particularly encouraging results, with objective response rates exceeding 90% at six months and median overall survival exceeding 30 months.[29] Median progression-free survival approached 20 months, comparing favorably with historical outcomes of anthracycline-based TACE.[29]

Collectively, these findings support the feasibility and potential efficacy of raltitrexed-eluting bead TACE (Table 1).[23–29] Nevertheless, it should be acknowledged that the current evidence base is dominated by retrospective analyses and single-arm studies, and well-designed randomized trials are required to establish definitive comparative benefit.

HAIC With Raltitrexed-Containing Regimens

HAIC is an established treatment option for patients with unresectable HCC, particularly those with extensive intrahepatic tumor burden, multifocal disease, or portal vein tumor thrombosis.[30,31] By delivering cytotoxic agents directly through the hepatic artery, HAIC achieves high intratumoral drug exposure while limiting systemic toxicity. The most widely studied HAIC regimen in HCC is oxaliplatin combined with 5-FU and leucovorin (FOLFOX-HAIC). However, the requirement for prolonged continuous infusion of 5-FU imposes a substantial treatment burden and increases the risk of catheter-related complications.

In this context, raltitrexed has emerged as an attractive alternative fluoropyrimidine substitute. Owing to its prolonged intracellular retention and short infusion requirement, raltitrexed can maintain antitumor activity while markedly reducing infusion time. Oxaliplatin–raltitrexed HAIC, initially developed in colorectal cancer,[32] has subsequently been applied to HCC.

Accumulating evidence from retrospective studies and prospective single-arm cohorts suggests that oxaliplatin–raltitrexed HAIC demonstrates clinically meaningful antitumor activity in unresectable HCC (Table 2).[33–45] Across reported studies, objective response rates ranged from approximately 30% to over 60%, with disease control rates frequently exceeding 70%. Median overall survival varied according to disease stage and concomitant treatments, generally ranging from 8 to more than 20 months, while median progression-free survival or time to progression ranged from approximately 5 to 13 months. Despite heterogeneity among studies, the consistency of these findings supports the clinical activity of raltitrexed-containing HAIC regimens.

Comparison Between Oxaliplatin–Raltitrexed HAIC and FOLFOX-HAIC

Several retrospective studies have directly compared oxaliplatin–raltitrexed HAIC with FOLFOX-HAIC in patients with advanced HCC.[40,42,44] Across these analyses, no significant differences were observed in objective response rate, progression-free survival, or overall survival.[40,42,44] Importantly, raltitrexed-based HAIC offers substantial practical advantages by reducing infusion time by approximately 46 hours per treatment cycle. This may shorten hospitalization, improve patient convenience, and reduce healthcare costs. These features make oxaliplatin–raltitrexed HAIC an attractive alternative to FOLFOX-HAIC, particularly in patients unsuitable for prolonged continuous infusion or in centers aiming to optimize HAIC workflow.

Combination of Raltitrexed-Based HAIC With Systemic Therapy

The integration of HAIC with systemic therapies, including TKIs and ICIs, represents a mechanistically rational strategy for the treatment of unresectable HCC.[46] It is speculated that HAIC may induce extensive tumor cell death and antigen

Table 1 Studies with Raltitrexed-Contained TACE for HCC

Study	Regimen	Design	TACE type	N	Age, y	Sex (M/F)	Stage	Tumor Size	Child-Pugh	Response	OS, m	PFS, m
Zhao 2016[23]	A: raltitrexed+OXA B: 5-FU+OXA C: DOX+OXA all followed OXA infusion	RCT	cTACE	76 76 75	55 (28–75) 54 (19–72) 55 (26–79)	63/13 71/5 67/8	B/C: 54/22 62/14 56/19	10.0±4.4 10.5±3.8 10.8±4.1	A/B: 66/10 61/15 59/16	CR/PR/SD/PD: 20/31/22/3 14/22/29/11 15/23/27/10*	mOS: 13.4 8.5 9.6*	mPFS: 6.7 4.6 4.9*
Shao 2019[24]	Raltitrexed, OXA infusion first	Prospective	cTACE	123	58 (38–77)	100/23	unresectable	≤/>10 cm: 89/34	A/B: 84/39	CR/PR/SD/PD: 10/43/65/5	mOS: 20.8	mPFS: 11.3
Qi 2020[26]	A: Raltitrexed B: DOX all OXA infusion first	Prospective	cTACE	150 150	57±9 58±7	108/42 112/38	I–II/III–IV: 65/85 71/79	NA	NA	CR/PR/SD/PD: 32/47/52/19 40/42/45/23#	1-year: 75.33% 76.00%#	NA
He 2021[25]	A: raltitrexed+LBP+THP B: LBP+THP	Retrospective	cTACE	92 92	51 (33–80) 53 (28–78)	88/4 84/8	B/C: 35/57 32/60	7 (2–17) 8 (3–15)	A/B: 80/12 81/11	CR/PR/SD/PD: 18/53/47/17 7/33/62/53*	mOS: 10 7*	6-m RFS: 35.9% 16.3%*
Bi 2022[27]	Raltitrexed, OXA or LBP infusion first	Retrospective	dTACE	41	58±11	31/10	A/B/C: 5/28/8	7.2±3.4	A/B: 30/11	CR/PR/SD/PD: 3/17/3/3 at 1 m	mOS: 43.7	mPFS: 21.6
Yang 2023[28]	A: THP B: raltitrexed C: arsenic trioxide	Retrospective	dTACE	34 34 34	60±7 62±8 60±7	22/12 29/5 26/8	PVTT or not: 23/11 21/13 20/14	NA	A/B: 24/10 26/8 23/11	ORR/DCR: 21/18 14/16 22/19#	mOS: 30.6 27.7 29.0#	mPFS: 10.6 9.0 10.3#
Sun 2024[29]	Raltitrexed	Prospective	dTACE	94	58±9	66/28	All stage B	5.1±4.3	A/B: 84/10	CR/PR/SD: 10/63/3	1, 2, 3-y: 95%, 82%, 44%	mTTP: 22.7 mPFS: 19.8

Notes: * P<0.05; # P>0.05.

Abbreviations: 5-FU, 5-fluorouracil; CR, complete response; DCR, disease control rate; DOX, doxorubicin; EPR, epirubicin; HCC, hepatocellular carcinoma; LBP, lobaplatin; ORR, objective response rate; OS, overall survival; OXA, oxaliplatin; PD, progressive disease; PFS, progression-free survival; PR, partial response; PVTT, portal vein tumor thrombus; SD, stable disease; TACE, transarterial chemoembolization; THP, pirarubicin; TTP, time to progression.

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Table 2 Studies with Raltitrexed-Contained HAIC for HCC

Study	Regimen	Design	TACE	N	Age, y	Sex (M/F)	Stage	Tumor Size	Child-Pugh	Response	OS, m	PFS, m
Cui 2017[33]	A: OXA+raltitrexed+EPR B: 5-FU+EPR+OXA (all TACE first)	Retrospective	cTACE	40 46	52±10 55±10	35/5 44/2	B/C: 15/25 13/33	≤/>10 cm: 30/10 33/13	A/B: 31/9 40/6	CR/PR/SD/PD: 0/1/15/22 1/1/12/31[#]	mOS: 7.4 5.8[#]	mPFS: 3.6 2.6*
Zhu 2018[34]	OXA+raltitrexed	Retrospective	cTACE	86	54 (31–84)	73/13	Major PVTT	≤/>10 cm: 46/40	A/B/C: 18/50/18	CR/PR/SD/PD: 0/45/20/21	mOS: 8.7 1, 2, 3-y: 40.7%, 22.1%, 8.1%	NA
Liu 2019[35]	OXA+raltitrexed	Retrospective	cTACE	37	57 (32–81)	33/4	B/C: 17/20	≤/>10 cm: 21/16	A/B: 30/7	CR/PR/SD/PD: 3/17/8/9	mOS: 19	mPFS: 12
Chen 2020[36]	OXA+raltitrexed	Prospective	No	39	53 (25–70)	34/5	B/C: 14/25	≤/>10 cm: 24/15	A/B: 32/7	CR/PR/SD/PD: 1/17/13/4	6, 12-m: 73.9%, 43.2%	mTTP: 6.7 mPFS: 5.2
Liao 2020[37]	A: OXA+raltitrexed B: Tegafur+THP (all followed by TACE)	Retrospective	cTACE	74 74	51 (31–79) 53 (16–78)	61/13 64/10	A/B/C: 6/33/35 15/24/35	</≥5 cm: 39/35 38/36	A/B: 66/8 72/2	CR/PR/SD/PD: 8/40/18/6 4/30/21/12*	mOS: 16.2 12.8*	NA
Chen 2022a[38]	OXA+raltitrexed (7 TKI/ICI)	Retrospective	No	52	55±10	51/1	B: 52	≤/>10 cm: 35/17	A/B: 42/10	CR/PR/SD/PD: 1/22/15/9	mOS: 17.0	mPFS: 5.8
Chen 2022b[38]	OXA+raltitrexed (7 TKI/ICI)	Retrospective	No	67	53±11	61/6	C: 67	≤/>10 cm: 37/30	A/B: 44/23	CR/PR/SD/PD: 0/26/24/10	mOS: 10.4	mPFS: 5.5
Wu 2022[39]	OXA+raltitrexed (all TKI, 22 ICI)	Retrospective	No	35	53±12	33/2	Advanced	8.4±4.5	A/B: 34/1	CR/PR/SD/PD: 0/4/16/15	mOS: 10	mTTP: 3.5
Zang 2023[40]	A: OXA+raltitrexed B: OXA+5-FU+leucovorin (all TKI+ICI)	Retrospective	No	42 40	50 (22–73) 46 (24–72)	38/4 38/2	B/C: 4/38 5/35	</≥10 cm: 17/25 12/28	A/B: 38/4 35/5	CR/PR/SD/PD: 0/18/18/6 0/17/18/5[#]	mOS[a]: 17.7 20.3[#]	mPFS[a]: 10.2 10.7[#]
Chen 2024[41]	OXA+raltitrexed (all TKI, 15 ICIs)	Prospective	No	39	52 (28–73)	31/8	C: 39	≤/>10 cm: 23/16	A/B: 32/7	CR/PR/SD/PD: 3/21/11/4	mOS: 11.3 6, 12-m: 81.7%, 44.1%	mPFS: 6.2
Tu 2024[42]	A: OXA+raltitrexed B: OXA+5-FU+leucovorin	Retrospective	TACE	60 74	54 (51–57) 52 (50–54)	65/9 55/5	C: 60 74	9 (8–10) 10 (9–11)	A/B: 50/10 54/20	CR/PR/SD/PD: 0/11/31/18 0/10/38/26[#]	mOS[b]: 10.8 8.7[#]	mPFS[b]: 10.0 7.1[#]
Lu 2025[43]	A: OXA+raltitrexed (TKI) B: cTACE using EPR	Retrospective	No cTACE	39 43	76±6 74±6	27/12 34/9	B/C: 25/14 26/17	8.2±3.1 7.5±2.8	A/B: 26/13 31/12	CR/PR/SD/PD: 9/15/8/7 2/14/9/18*	mOS: 18.1 10.6*	mPFS: 9.2 4.6*
Tan 2025[44]	A: OXA+raltitrexed B: OXA+5-FU+leucovorin (all TKI+ICI+radiotherapy)	Retrospective	No	21 21	54±10 56±8	19/2 19/2	C: 21 21	10.1±4.1 8.9±3.4	A/B: 16/5 15/6	CR/PR/SD/PD: 2/13/4/2 1/14/6/0[#]	mOS[c]: 15.5 14.6[#]	mPFS[c]: 12.7 12.5[#]
Zang 2025[45]	OXA+raltitrexed (all TKI+ICI)	Prospective	No	39	55 (34–73)	35/4	B/C: 3/36	</≥10 cm: 13/26	A/B: 37/2	CR/PR/SD/PD: 5/28/5/1	mOS: 21.2 6, 12-m: 94.9%, 76,9%	mPFS: 13.8

Notes: [a] The median PFS in the FOLFOX HAIC group was 10.7 months and 10.2 months in the RALOX HAIC group (HR, 0.79; 95% CI, 0.46–1.38; P = 0.41). The median OS was 20.3 months in the FOLFOX HAIC group and 17.7 months in the RALOX HAIC group (HR, 0.81; 95% CI, 0.44–1.51; P = 0.50). [b] The median PFS was 10.2 months in the RALOX HAIC group (95% CI 7.69–12.36 months) and 7.07 months in the FOLFOX HAIC group (95% CI 5.28–8.85 months; P = 0.102). The median OS was 10.82 months in the RALOX HAIC group (95% CI, 8.80–12.85 months) and 8.67 months in the FOLFOX HAIC group (95% CI, 7.11–10.22 months; P = 0.066). [c] The median PFS was 12.7 months in the RALOX HAIC group and 12.5 months in the FOLFOX HAIC group (HR, 0.792; 95% CI, 0.359–1.748; P = 0.564). The median OS was 15.5 months in the RALOX HAIC group and 14.6 months in the FOLFOX HAIC group (HR, 0.998; 95% CI, 0.438–2.274; P = 0.995). * P<0.05; [#] P>0.05.

Abbreviations: 5-FU, 5-fluorouracil; CR, complete response; EPR, epirubicin; HCC, hepatocellular carcinoma; ICI, immune checkpoint inhibitors; OS, overall survival; OXA, oxaliplatin; PD, progressive disease; PFS, progression-free survival; PR, partial response; PVTT, portal vein tumor thrombus; SD, stable disease; TACE, transarterial chemoembolization; THP, pirarubicin; TKI, tyrosine kinase inhibitors; TTP, time to progression.

release, potentially priming antitumor immune responses,[47] while systemic agents sustain and amplify these effects through immune modulation and vascular normalization.[48–50]

Recent prospective single-arm phase II studies have provided proof-of-concept evidence supporting this approach. In patients with advanced HCC and extrahepatic metastasis who had progressed on prior systemic therapy, apatinib combined with oxaliplatin–raltitrexed HAIC achieved objective response rates exceeding 50% and meaningful survival outcomes.[41] Similarly, combination therapy with lenvatinib, camrelizumab, and oxaliplatin–raltitrexed HAIC yielded high response rates and prolonged progression-free and overall survival in patients with unresectable HCC.[45] Although limited by their non-randomized design, these studies suggest that raltitrexed-based HAIC may serve as an effective backbone for combination strategies incorporating targeted therapy and immunotherapy.

At present, reliable biological biomarkers for predicting therapeutic response to HAIC in HCC remain unavailable. In this context, emerging evidence suggests that TS is intrinsically overexpressed in HCC and may be associated with aggressive tumor behavior. Prior studies have shown that increased TS expression in HCC correlates with tumor differentiation, poorer survival, and metastatic potential, supporting the biological relevance of TS in HCC progression.[51,52] Given that raltitrexed directly targets TS, it is biologically plausible that baseline TS expression may influence sensitivity to oxaliplatin–raltitrexed HAIC. However, this hypothesis has not yet been directly tested in clinical studies. Future work should therefore evaluate whether intratumoral TS expression can serve as a predictive biomarker to refine patient selection and optimize the use of raltitrexed-based arterial therapies in HCC.

Safety

The safety profile of raltitrexed has been extensively characterized in colorectal cancer and provides an important framework for its application in HCC.[53] In arterial-based therapies, raltitrexed-containing regimens demonstrate a predictable and generally manageable toxicity profile.[40,42,44] Clinically significant myelosuppression is uncommon, gastrointestinal toxicity is usually mild, and transient elevations in liver enzymes are typically reversible. Importantly, raltitrexed lacks the cardiotoxicity associated with fluoropyrimidines,[54] which is a clinically relevant advantage in patients with cardiovascular comorbidities. Given its renal elimination, careful assessment of renal function and appropriate dose adjustment remain essential to minimize the risk of severe toxicity.[55]

Compared with FOLFOX-HAIC, oxaliplatin–raltitrexed HAIC appears to retain a broadly comparable safety profile while potentially reducing some treatment-related discomfort. In populations with a substantial burden of underlying cirrhosis, liver-related toxicities were generally similar between regimens, with no significant between-group differences in elevated ALT/AST, hypoalbuminemia, jaundice, or hepatic failure; moreover, HAIC-associated hepatic dysfunction was usually transient and relieved within one week in most patients.[40,42] Grade 3/4 toxicities also appeared comparable, particularly for thrombocytopenia, leukocytopenia, and severe transaminase elevation; in one series, grade 3/4 ALT increase was 7.5% with FOLFOX versus 7.1% with oxaliplatin–raltitrexed, and grade 3/4 AST increase was 12.5% versus 9.5%, respectively.[40] In addition, renal impairment did not seem to increase with raltitrexed-based treatment.[42] More recent data further suggest that oxaliplatin–raltitrexed HAIC may be associated with lower rates of abdominal pain and fever.[44]

Conclusions

Raltitrexed represents a mechanistically rational and increasingly utilized component of arterial-based therapies for hepatocellular carcinoma. Its direct inhibition of thymidylate synthase, prolonged intracellular retention, and short infusion schedule confer important pharmacological and logistical advantages over 5-fluorouracil, particularly in the settings of TACE and HAIC. Accumulating clinical evidence suggests that raltitrexed-based regimens achieve antitumor activity comparable to established chemotherapy protocols and may serve as an effective backbone for combination strategies with targeted therapy and immunotherapy. However, most available data are derived from retrospective analyses and single-arm studies, and definitive comparative benefit over conventional regimens has yet to be established. Well-designed randomized trials and biomarker-driven approaches are required to define the optimal role of raltitrexed in the management of unresectable HCC.

Disclosure

The authors report no conflicts of interest in this work.

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