IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

ANGIOGENSIS IN METASTATIC COLORECTAL CANCER AND TARGETED THERAPY

Dr.R.Dinesh Kumar[1], and Jesni Jaison[2] ,Jiby Remola Job[2], Mohammed Rashid. P[2].

1. **Asst.professor, Department of Pharmacy Practice, The Erode College of Pharmacy , TamilNadu**
2. **Doctor of Pharmacy , The Erode College of Pharmacy , TamilNadu**

ABSTRACT

Targeting tumor-driven angiogenesis is a successful method for treating metastatic colorectal cancer (mCRC); however, the availability of multiple medicines, the incidence of resistance, and the paucity of data make selecting a second-line therapy difficult. Numerous prognostic and predictive biomarkers that have been verified The use of in this review is looked at. Second-line management with angiogenesis-targeted medicines Angiogenesis, or the formation of new blood vessels, has been targeted for the treatment of colorectal and other cancers through a variety of pathways and molecules. Angiogenesis is thought to be mediated by the binding of vascular endothelial growth fact Therapy for metastatic colorectal cancer (m CRC) has evolved significantly since the late 1990s, and now includes a combination of doublet or triplet chemotherapy and a targeted agent. Angiogenesis, or the formation of new blood vessels, can be targeted a crucial component of the overall treatment plan Since the first anti-angiogenesis drug was approved in 2004,multiple drugs or (VEGF)-A to VEGF receptor (VEGFR)-2. VEGF pathways in other animals VEGF-A, VEGF-B, and placental GR all play a role in angiogenesis.

Keywords:

Angiogenesis, Vascular endothelial growth factor, Colorectal cancer,

INTRODUCTION

Current colon therapy

Colorectal cancer (CRC) is one of the world's most lethal and common cancers, accounting for nearly 881,000 cancer-related deaths in 2018. For many years, surgery and chemotherapy have been the treatment of choice for cancer patients. However, the prognosis for CRC patients has never been good, particularly for those with metastatic lesions. Targeted therapy is a new treatment option that has successfully extended overall survival in patients with CRC. Following the success of anti-EGFR (epidermal growth factor receptor) drugs, New agents blocking different critical pathways include the anti-GFR agent cetuximab and the anti-angiogenesis agent

bevacizumab. Immune checkpoints and pathways are emerging at an unprecedented rate. On the basis of an increasing number of high-quality clinical trials, global guidelines are currently updating the recommended targeted drugs. This review discusses the limitations and future trends of existing CRC-targeted agents, as well as their underlying mechanisms.

Chemotherapy

Current chemotherapy includes both single-agent therapy, mainly fluoropyrimidine (5-FU)-based, and multiple-agent regimens containing one or several drugs. The combined therapy is associated with certain limitations, such as existing systemic toxicity, unsatisfying response rate, unpredictable innate and acquired resistance, and low tumor-specific selectivity. has been shown to be more effective than, which is infrequently applied because of its potential increased toxicity

Targeted therapy

Small molecules, such as monoclonal antibodies, are major players in targeted therapies. Antibodies work within cells to inactivate selected enzymes, thereby interfering with tumor cell growth and even triggering apoptosis. Carfilzomib for multiple myeloma, ribociclib for metastatic breast cancer, and rucaparib for BRCA-positive ovarian cancer are some of the examples.

METHODS AND MATERIALS

A total of 46 patients (20 men and 26 women) with complete clinical data the primary CRC and the corresponding metastatic sites (lymph nodes and liver). Patients ranged in age from 40 to 82 years old, with a median age of 62. The patients' clinical and histopathological characteristics are observed. All of the patients contributed tissues, including primary tumor’s and metastases that were matched.

The patients are grouped and different drugs were administrated

RESULT

AGENT	DESIGN	SUBJECT	TREATMENT	RESULT
Bevacizumab	Phase 3	mCRC First line therapy	Capecitabine + Beva	NA NA
Bevacizumab	Phase 3	Mcrc	FOLFOXIRI + Bev FOLFIRI + Beva	NA NA
Bevacizumab	Phase 3	mCRC	Beva + capecitabine	19%
Bevacizumab	Phase 3	mCRC untreated	Capecitabine Beva + IFL	10% 44.8%
Bevacizumab	Phase 3	mCRC second line	Placebo + IF FOLFOX + Bev	34.8% 22.7%
Bevacizumab	Phase 3	mCRC second line	FOLFOX Beva Beva + chemo Chemo	8.6% 3.3% 2.8%
Regorafenib	Phase 3	mCRC Treatment refactory	Regorafenib Placebo	2.0% 4%
Regorafenib	Phase3	mCRC Treatment refactory	Regorafenib Placebo	0% 1%
Zivaflibercept	Phase3	mCRC Treatment refactory	FOLFIRI+ aflibercept	19.8%

Anti-VEGFR agents

until now, only bevacizumab has been approved by the FDA as a first- and second-line VEGF-targeted agent for CRC, though new agents are being developed, and some of them have already been approved. They've been given the green light to treat CRC as a second-line treatment .

Aflibercept is a VEGFR-1 and VEGF-2 extracellular domain fusion protein. It acts as a ligand trap targeting the proteins,, and PIGF. The single-agent benefit of aflibect seems to be limited, while chemo-combinations showed great potential. In the first-line setting, the combination of

a flibercept with FOLFOX did not result in noticeable benefits in PFS or response rate, but did result in increased adverse event rates.

Ramucirumab, a fully humanized monoclonal VEGFR-2-\ntargeted IgG antibody, is another FDA-approved drug for the second-line treatment of metastatic cancer. In a second trial, a combination of ramuciruab and FOLFIRI

significantly prolonged PFS Similar to the findings with aflibercept, a phase II trial showed that the FOLFOX regimen may not benefit in terms of PFS.

New TKIs expressing remarkable antitumor effects in preclinical studies have produced unsatisfying OS and RR values in recent reports. PFS may be prolonged by drugs such as the brivanib212 and cediranib, a TKI targeted to all three VEGFRs and PDGFR that failed to present efficacy towards control of colorectal carcinoma (CRC) The drug nintedanib has no indication or supporting data for treating the disease.

Resistance to antiangiogenic therapy.

Anti-VEGF resistance has been observed in a variety of cancers, including CRC, which could be due to compensatory activation of other signalling pathways and alternative excretion of angiogenesis-related proteins.

DISCUSSION

Bevacizumab and cetuximab in a combined regimen with FOLFIRI. No obvious difference was discovered in the response rate or PFS for both arms, yet OS was prolonged in the cetoximab arm. The first head-to-head comparison study was the phase III FIRE-3 trial, which compared bevacizumaab and Cetuximob. In a recent phase III trial combining these two agents with FOLFOX/FOLFIRI therapy, similar results were observed.There were few differences in response rate, PFS, and OS between the two groups, according to the study.191 The PEAK trial, which is centred on panitumumab and bevacizumab with FOLFOX, according to the manufacturer.The response rate and PFS appeared to be similar, with a slightly longer OS for bevacizumab vs. panitumumab.

The genetic heterogenicity of cancer has been identified, together with a comprehensive understanding of the different molecular pathways and genetic profiles involved. The NCCN recommended strategy for targeting specific enzymes, growth receptors, and signal transducers makes personalized cancer therapy possible. There is no universal regimen that can easily treat every patient with equal efficacy. Targeted therapy is associated with prolonged survival, but there are several drawbacks. The cost–benefit balance is questionable when current chemotherapy is much less expensive than extra targeted regimens. Efficacy differs dramatically among people, leading to increased burdens associated with patient selection and surveillance.

CONCLUSION

Targeted therapy is associated with prolonged survival, but there are several drawbacks. The cost–benefit balance is questionable when current chemotherapy is much less expensive than extra targeted regimens. Efficacy differs dramatically among people, leading to increased burdens associated with patient selection and surveillance. Current drug resistance cannot be avoided, and acquired resistance adds further complications.

REFERENCE

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin.* 2018;68:394–424. doi: 10.3322/caac.21492. [PubMed] [CrossRef] [Google Scholar]

2. Song X, Zhao Z, Barber B, Gregory C, Schutt D, Gao S. Characterizing medical care by disease phase in metastatic colorectal cancer. *Am J Manag Care.* 2011;17(Suppl 5):SP20–SP25. [PubMed] [Google Scholar]

3. Devesa H, Pereira L, Gonçalves A, Brito T, Almeida T, Torres R, Midoes A. Axillary lymph node metastasis of colon cancer-case report and literature review. *Case Rep Clin Med.* 2014;12:669–673. doi: 10.4236/crcm.2014.312141. [CrossRef] [Google Scholar]

4. Kirstein MM, Lange A, Prenzler A, Manns MP, Kubicka S, Vogel A. Targeted therapies in metastatic colorectal cancer: A systematic review and assessment of currently available data. *Oncologist.* 2014;19:1156–1168. doi: 10.1634/theoncologist.2014-0032. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

5. Kim DH, Sung B, Kang YJ, Hwang SY, Kim MJ, Yoon JH, Im E, Kim ND. Sulforaphane inhibits hypoxia-induced HIF-1α and VEGF expression and migration of human colon cancer cells. *Int J Oncol.* 2015;47:2226–2232. doi: 10.3892/ijo.2015.3200. [PubMed] [CrossRef] [Google Scholar]

6. Ajith TA. Current insights and future perspectives of hypoxia-inducible factor targeted therapy in cancer. *J Basic Clin Physiol Pharmacol.* 2018;30:11–18. doi: 10.1515/jbcpp-2017-0167. [PubMed] [CrossRef] [Google Scholar]

7. Semenza GL. HIF-1 mediates metabolic responses to intratumoral hypoxia and oncogenic mutations. *J Clin Invest.* 2013;123:3664–3671. doi: 10.1172/JCI67230. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

8. Nieves BJ, D'Amore PA, Bryan BA. The function of vascular endothelial growth factor. *Biofactors.* 2009;35:332–337. doi: 10.1002/biof.46. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

9. Iwasaki K, Yabushita H, Ueno T, Wakatsuki A. Role of hypoxia-inducible factor-1α, carbonic anhydrase-IX, glucose transporter-1 and vascular endothelial growth factor associated with lymph node metastasis and recurrence in patients with locally advanced cervical cancer. *Oncol Lett.* 2015;10:1970–1978. doi: 10.3892/ol.2015.3524. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

10. Brahimi-Horn MC, Chiche J, Pouyssegur J. Hypoxia and cancer. *J Mol Med (Berl)* 2007;85:1301–1307. doi: 10.1007/s00109-007-0281-3. [PubMed] [CrossRef] [Google Scholar]

11. Cohen SA, Yu M, Baker K, Redman M, Wu C, Heinzerling TJ, Wirtz RM, Charalambous E, Pentheroudakis G, Kotoula V, et al. The CpG island methylator phenotype is concordant between primary colorectal carcinoma and matched distant metastases. *Clin Epigenetics.* 2017;9:46. doi: 10.1186/s13148-017-0347-1. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

12. Luo KJ, Hu Y, Wen J, Fu JH. CyclinD1, p53, E-cadherin, and VEGF discordant expression in paired regional metastatic lymph nodes of esophageal squamous cell carcinoma: A tissue array analysis. *J Surg Oncol.* 2011;104:236–243. doi: 10.1002/jso.21921. [PubMed] [CrossRef] [Google Scholar]

13. Knosel T, Schluns K, Dietel M, Petersen I. Chromosomal alterations in lung metastases of colorectal carcinomas: Associations with tissue specific tumor dissemination. *Clin Exp Metastasis.* 2005;22:533–538. doi: 10.1007/s10585-005-5239-7. [PubMed] [CrossRef] [Google Scholar]

14. Wu Y, Jin M, Xu H, Shimin Z, He S, Wang L, Zhang Y. Clinicopathologic significance of HIF-1α, CXCR4, and VEGF expression in colon cancer. *Clin Dev Immunol.* 2010;2010(pii):537531. [PMC free article] [PubMed] [Google Scholar]

15. Qiu Y, Zhou H. Expression of HIF-1alpha and VEGF in human laryngeal carcinoma and its relationship with angiogenes. *Lin Chung Er Bi Yan Hou Tou Jing Wai Ke Za Zhi*. 2014;28:389–393. (In Chinese) [PubMed] [Google Scholar]

16. Tournigand, C. et al. FOLFIRI followed by FOLFOX6 or the reverse sequence in

advanced colorectal cancer: a randomized GERCOR study. J. Clin. Oncol. 22,

229–237 (2004).

17. Vera, R. et al. Current controversies in the management of metastatic colorectal

cancer. Cancer Chemother. Pharm. 76, 659–677 (2015).

18. Falcone, A. et al. Phase III trial of infusional fluorouracil, leucovorin, oxaliplatin,

and irinotecan (FOLFOXIRI) compared with infusional fluorouracil, leucovorin,

and irinotecan (FOLFIRI) as first-line treatment for metastatic colorectal cancer:

the Gruppo Oncologico Nord Ovest. J. Clin. Oncol. 25, 1670–1676 (2007).

19. Souglakos, J. et al. FOLFOXIRI (folinic acid, 5-fluorouracil, oxaliplatin and irinotecan) vs FOLFIRI (folinic acid, 5-fluorouracil and irinotecan) as first-line treatment in metastatic colorectal cancer (MCC): a multicentre randomised phase III

trial from the Hellenic Oncology Research Group (HORG). Br. J. Cancer 94,

798–805 (2006).

20. Cassidy, J. et al. XELOX (capecitabine plus oxaliplatin): active first-line therapy for

patients with metastatic colorectal cancer. J. Clin. Oncol. 22, 2084–2091 (2004).

21. Goldberg, R. M. et al. A randomized controlled trial of fluorouracil plus leucovorin, irinotecan, and oxaliplatin combinations in patients with previously

untreated metastatic colorectal cancer. J. Clin. Oncol. 22, 23–30 (2004).

22. Brodsky, F. M. Monoclonal antibodies as magic bullets. Pharm. Res. 5, 1–9 (1988).

23. Lee, Y. T., Tan, Y. J. & Oon, C. E. Molecular targeted therapy: treating cancer with

specificity. Eur. J. Pharm. 834, 188–196 (2018).

24. Oh, D. Y. & Bang, Y. J. HER2-targeted therapies—a role beyond breast cancer.

Nat. Rev. Clin. Oncol. 17, 33–48 (2020).

25. Ferguson, F. M. & Gray, N. S. Kinase inhibitors: the road ahead. Nat. Rev. Drug

Discov. 17, 353–377 (2018).

26. Tariman, J. D. Changes in cancer treatment: Mabs, Mibs, Mids, Nabs, and Nibs.

Nurs. Clin. N. Am. 52, 65–81 (2017).

27. Tiwari, A., Saraf, S., Verma, A., Panda, P. K. & Jain, S. K. Novel targeting

approaches and signaling pathways of colorectal cancer: An insight. World J.

Gastroenterol. 24, 4428–4435 (2018).

28. Krishnamurthy, N. & Kurzrock, R. Targeting the Wnt/beta-catenin pathway in

cancer: update on effectors and inhibitors. Cancer Treat. Rev. 62, 50–60 (2018).

29. Arteaga, C. L. & Engelman, J. A. ERBB receptors: from oncogene discovery to basic science to mechanism-based cancer therapeutics. Cancer Cell 25, 282–303 (2014).

30. Tebbutt, N., Pedersen, M. W. & Johns, T. G. Targeting the ERBB family in cancer: couples therapy. Nat. Rev. Cancer 13, 663–673 (201)