META-ANALYSIS OF PHASE II TRIALS USING BEVACIZUMAB WITH STANDARD FLUOROPYRIMIDINE BASED NEOADJUVANT CHEMORADIOThERAPY IN PATIENTS WITH LOCALLY ADVANCED RECTALCancer

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Introduction: Bevacizumab (an anti-VEGF antibody) is increasingly being used with neoadjuvant regime for the curative treatment of locally advanced rectal cancers however its efficacy has only been reported in small trials. This meta-analysis aims to assess the efficacy of bevacizumab as part of the neoadjuvant regime to induce complete pathological response and facilitate sphincter-preserving surgery and to assess whether the efficacy justifies the potential increased risk of toxicity and surgical complications.

Methods: A comprehensive literature search was undertaken using Pubmed, EMBASE and Medline using the search terms ‘rectal cancer’, ‘bevacizumab’ and ‘trials’, Back referencing and hand search complimented retrieval of suitable articles. For the purpose of this analysis, we included only phase II trials, reported in english language, involving the addition of bevacizumab to standard fluoropyrimidine-based neoadjuvant chemoradiotherapy (NCRT) in patients with curable locally-advanced rectal cancer (LARC). We excluded any trials using bevacizumab with unconventional NCRT regimes or short-course radiotherapy and as complimentary to adjuvant therapy. We performed pooled analysis of selected data to ascertain weighted pooled proportion for study end-points. Appropriate model (fixed vs random effect) was selected dependent of test for heterogeneity. Statistical analysis was performed using Open Meta Analyst.

Results: A total of 13/127 articles satisfied the inclusion criteria. The cumulative sample size of these studies was 510 patients. In a pooled analysis, the weighted cumulative pathological complete response rate was 20.2% (95%CI 0.158, .0247, p <0.001), grade 3/4 toxicity rate was 35.5% (95%CI 0.229, 0.481, p 0.001), the curative operation rate was 98% (95%CI 0.969,992, p 0.006). The R0 resection was reported in 5/13 studies with cumulative rates of 88.4% (95%CI 0.786, 0.982, p <0.001), the sphincter saving surgery was reported in 4/13 studies with cumulative rates of 63% (95%CI 0.506, 0.754, p <0.001). The post-operative complication were reported in 6/13 studies with cumulative rates of 31.7% (95%CI 0.21, 0.424, p < 0.001). Long term prognosis was available in 3 studies not suitable for analysis.

Conclusion: The addition of bevacizumab to neoadjuvant regimes modestly increases the pathological completion rate without compromise in grade T3-T4 toxicity. There is no improvement in the rate of sphincter-preserving surgery or R0 resections and modest rise in post-operative complications. Overall, we did not find any additional benefit of adding bevacizumab to standard NCRT however, further larger trials with longer follow-up period may help support its efficacy and decipher long-term prognosis.