The need for effective radiosentitizing agents: experience in patients with complete pathological response

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Chemoradiation therapy is now considered the preferred initial treatment strategy for distal rectal cancer because of the observation of better local disease control and significant tumor downstaging. Downstaging has become an important clinical outcome as patients with complete pathological response are associated with improved survival. Even though radiation alone may result in low local recurrence rates, the use of additional radiosensitizing agents may provide an increase in local disease control in addition to improved tumor regression rates. Several compounds have been investigated in the setting of neoadjuvant multimodality treatment of rectal cancer with variable rates of treatment-related toxicity and complete pathological response. The balance between complete pathological response and toxicity should aid in the management decision for the use of radiosensitizing agents in the neoadjuvant setting for the treatment of rectal cancer. ***Anti-Cancer Drugs*** **22:308–310 © 2011 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

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Introduction

One of the most significant challenges in the management of rectal cancer has been in achieving adequate local disease control, particularly after radical surgery. Even though meticulous total mesorectal excision of rectal cancers may provide low local recurrence rates, several patients may harbor tumors that may benefit from additional treatment [1,2]. In fact, even in the hands of experts in total mesorectal excision, surgery alone has resulted in adequate local failure rates (< 3%) only in high, mobile, and small tumors. Low-lying, fixed, and large lesions were associated with a significantly higher (17%) local recurrence rate [3].

In this setting, the addition of radiation therapy (RT) with or without chemotherapy has become the preferred treatment strategy for locally advanced tumors invading through the rectal wall or in the presence of lymph node metastases [4]. The observation of improved local disease control associated with the use of RT before radical surgery led many institutions worldwide to adopt the neoadjuvant approach as the preferred initial treatment strategy. In addition to the benefits of local disease control, neoadjuvant treatment regimens with the use of concomitant chemotherapy, believed to be a radiosensitizer, were shown to be associated with significant tumor downstaging and downsizing. In a proportion of these patients, tumor regression could result in complete pathological response (pCR), with the absence of residual cancer cells in the resected specimen. In some patients, tumor regression could be so significant resulting in a greater chance for a sphincter-preserving procedure or even the chance for an alternative procedure to total mesorectal excision [5,6]. Still, pCR seems to be associated with excellent local disease control and improved survival when compared with incomplete pathological response [7]. The validity of using pCR as an outcome for rectal cancer may be questioned by the potential bias created by the variability in chemoradiotherapy (CRT) regimens, pathological procedures used for assessment, and radiological staging of patients undergoing treatment. Still, it remains a clinically relevant assessment because of the survival advantage of these patients and to the potential use of less aggressive therapies other than total mesorectal excision. For these reasons, the search for regimens and radiosenstizing agents capable of increasing complete tumor response rates are highly desirable.

Short-course and long-course chemoradiation

Even though the benefits in local disease control seem to be equivalent between short-course RT and long-course chemoradiation therapy [8], there are significant differences in terms of tumor downstaging observed between patients undergoing these two regimens. In patients undergoing short-course RT, the rates of pCR are significantly lower when compared with patients undergoing long-course neoadjuvant chemoradiation. However, when one compares these two regimens, the addition of chemotherapy is not the sole difference. Timing between RT completion and surgery is also different between these two regimens and may have contributed to the differences seen in tumor downstaging. In patients undergoing short-course RT, surgery is performed usually 1 week after

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RT completion whereas long-course CRT is followed by radical surgery after at least 6–8 weeks. The fact is that tumor downstaging seems to be a time-dependent effect. Even in patients undergoing neoadjuvant CRT, longer intervals between RT completion and surgery have been associated with significant increases in pCR and improved outcomes [9–11]. In an interesting review of patients undergoing neoadjuvant CRT from a single institution, there was a significant rise in the rates of pCR after 7 weeks from RT completion with stabilization of such increase in pCR rates after 12 weeks [10]. This improved downstaging effect observed over time seems not to be restricted to long-course CRT. The association of short-course RT followed by delayed surgery (6–8 weeks after RT completion instead of the usual 7 days) led patients with cT4 considered unresectable tumors to more than 80% R0 resections with this hybrid strategy [12].

But timing is probably not the sole predictor of tumor downstaging, and the use of radiosensitizing agents may play a role in such phenomena.

Radiosensitizing agents

The comparison of patients with locally invasive rectal cancers treated with either neoadjuvant RT alone (45 Gy) or chemoradiation (45 Gy) with 5-fluorouracil (5-FU) and leucovorin showed a significant benefit in terms of long-term local disease control. In fact, patients benefited from the use of chemotherapy even if this was delivered postoperatively. However, even more important was the fact that patients that were treated with CRT preoperatively were associated with higher rates of pCR (13 vs. 5%; $P < 0.001$), higher rates of node-negative disease (ypN0), decreased tumor size (< 17%), and less risk of vascular invasion within the resected specimen [13,14]. Therefore, not only timing is important but the use of radiosensitizers may significantly impact pCR rates and its direct consequences on local disease control and long-term survival.

In a review of all phase II and phase III studies using variable neoadjuvant chemoradiation therapy regimens for rectal cancer, three factors were found to significantly influence the rates of pCR among the 71 studies including approximately 4000 patients: the method of 5-FU delivery, the use of additional drugs, and the dose of RT. The use of continuous infusional therapy with 5-FU, the use of combination of chemotherapy agents, and the delivery of RT dose of more than 45 Gy were all significant predictors of pCR, which was observed in up to 42% of patients [15]. In this study, a great deal of interest was shown in the use of combination chemotherapy agents in the neoadjuvant setting. An additional finding of this study was the fact that there was a trend toward increased pCR rates among patients who underwent CRT with oral 5-FU (capecitabine). This agent not only seems to be more convenient and tolerable to patients, but may also mimic continuous venous infusion of 5-FU, a recognized predictive factor for pCR [16].

The observation of excellent results in the use of oxaliplatin, particularly in metastatic disease from colorectal cancer, prompted its use in the neoadjuvant approach, in combination with 5-FU. With the hope of improving pCR rates, a randomized study comparing RT, capecitabine (oral 5-FU) with or without oxaliplatin was carried out in patients with locally advanced rectal cancer. Surprisingly, not only did the use of oxaliplatin not significantly improve pCR rates among patients, but it also led to a significant increase in treatment-related toxicity (25 vs. 1% in grade III/IV toxicity) [17].

Even more recently, the observation of significant activity of targeted biological drugs, such as bevazicumab and cetuximab, led to its utilization in phase I and phase II trials in the neoadjuvant setting. But the expected increase in pCR rates among patients undergoing this 'triple' therapy (5-FU, oxaliplatin, and cetuximab) was not observed in any of the trials. A recent review of these trials suggested a subadditive interaction between capecitabine, oxaliplatin, and cetuximab as reflected by decreased rates of pCR (9 vs. 16%) and significant tumor regression grades (more than 50% of tumor regression) among surgical specimens from these patients when compared with patients undergoing treatment with capecitabine and oxaliplatin alone [18]. It is not clear whether the inclusion of patients according to the Kras status has any influence in response to neoadjuvant CRT with this triple approach [19].

Recognizing the significant influence of the use of 5-FU in the neoadjuvant setting, our group has conducted a study using additional chemotherapy cycles not only during the RT therapy course, but also during the interval between RT completion and assessment of tumor response or surgery. With this approach, instead of using standard cycles of 5-FU-based chemotherapy at the beginning and the end of RT delivery, patients are treated with bolus 5-FU and leucovorin in 3-day cycles, given every 21 days, in a total of six cycles given during a 15-week period (6 weeks of CRT therapy and 9 weeks of interval of chemotherapy alone). Considering the fact that the effects of RT are time-dependent and that downstaging may still go on until 12 weeks from RT completion, the use of additional cycles during that particular interval could be beneficial for improving potential sensitizing effects of 5-FU. In fact, preliminary results of this study in a limited number of patients resulted in surprisingly high complete tumor response rates of more than 60% (compared with the earlier 27% obtained with standard 5-FU and leucovorin in two cycles) [20].

Conclusion

The identification of specific molecular and genetic abnormalities in these rectal tumors may provide additional information with regard to response to RT and to

specific radiosensitizing agents. This would allow identification of patients that are ideal candidates for RT alone, chemoradiation therapy, and with the use of specific agents according to individual genetic features. Even though there are several drugs known to be active in colorectal cancer, there is still a need for the development of new agents capable of increasing sensitivity of tumors and perhaps maximizing complete tumor response leading to improved oncological outcomes and to the possibility of minimally invasive surgical approaches of these patients.

References

1 Colquhoun P, Wexner SD, Cohen A. Adjuvant therapy is valuable in the treatment of rectal cancer despite total mesorectal excision. *J Surg Oncol* 2003; **83**:133–139.

2 Heald RJ, Ryall R. Recurrent cancer after restorative resection of the rectum. *Br Med J (Clin Res Ed)* 1982; **284**:826–827.

3 Simunovic M, Sexton R, Rempel E. Optimal preoperative assessment and surgery for rectal cancer may greatly limit the need for radiotherapy. *Br J Surg* 2003; **90**:999–1003.

4 Tjandra JJ, Kilkenny JW, Buie WD. Practice parameters for the management of rectal cancer (revised). *Dis Colon Rectum* 2005; **48**:411–423.

5 Sauer R, Becker H, Hohenberger W. Preoperative versus postoperative chemoradiotherapy for rectal cancer. *N Engl J Med* 2004; **351**:1731–1740.

6 Pucciarelli S, Capirci C, Emanuele U. Relationship between pathologic T-stage and nodal metastasis after preoperative chemoradiotherapy for locally advanced rectal cancer. *Ann Surg Oncol* 2005; **12**:111–116.

7 Maas M, Nelemans PJ, Valentini V. Long-term outcome in patients with a pathological complete response after chemoradiation for rectal cancer: a pooled analysis of individual patient data. *Lancet Oncol* 2010; **11**:835–844.

8 Bujko K, Nowacki MP, Nasierowska-Guttmejer A. Long-term results of a randomized trial comparing preoperative short-course radiotherapy with preoperative conventionally fractionated chemoradiation for rectal cancer. *Br J Surg* 2006; **93**:1215–1223.

9 Tulchinsky H, Shmueli E, Figer A. An interval >7 weeks between neoadjuvant therapy and surgery improves pathologic complete response and disease-free survival in patients with locally advanced rectal cancer. *Ann Surg Oncol* 2008; **15**:2661–2667.

10 Kalady MF, De Campos-Lobato LF, Stocchi L. Predictive factors of pathologic complete response after neoadjuvant chemoradiation for rectal cancer. *Ann Surg* 2009; **250**:582–589.

11 Kerr SF, Norton S, Glynne-Jones R. Delaying surgery after neoadjuvant chemoradiotherapy for rectal cancer may reduce postoperative morbidity without compromising prognosis. *Br J Surg* 2008; **95**:1534–1540.

12 Radu C, Berglund A, Pahlman L. Short-course preoperative radiotherapy with delayed surgery in rectal cancer–a retrospective study. *Radiother Oncol* 2008; **87**:343–349.

13 Bosset JF, Calais G, Mineur L. Enhanced tumorocidal effect of chemotherapy with preoperative radiotherapy for rectal cancer: preliminary results–EORTC 22921. *J Clin Oncol* 2005; **23**:5620–5627.

14 Bosset JF, Collette L, Calais G. Chemotherapy with preoperative radiotherapy in rectal cancer. *N Engl J Med* 2006; **355**:1114–1123.

15 Sanghera P, Wong DW, McConkey CC. Chemoradiotherapy for rectal cancer: an updated analysis of factors affecting pathological response. *Clin Oncol (R Coll Radiol)* 2008; **20**:176–183.

16 Ben-Josef E. Capecitabine and radiotherapy as neoadjuvant treatment for rectal cancer. *Am J Clin Oncol* 2007; **30**:649–655.

17 Gerard JP, Azria D, Gourgou-Bourgade S. Comparison of two neoadjuvant chemoradiotherapy regimens for locally advanced rectal cancer: results of the phase III trial ACCORD 12/0405-Prodige 2. *J Clin Oncol* 2010; **28**:1638–1644.

18 Weiss C, Arnold D, Dellas K. Preoperative radiotherapy of advanced rectal cancer with capecitabine and oxaliplatin with or without cetuximab: a pooled analysis of three prospective phase I–II trials. *Int J Radiat Oncol Biol Phys* 2010; **78**:472–478.

19 Glynne-Jones R, Mawdsley S, Harrison M. Cetuximab and chemoradiation for rectal cancer: is the water getting muddy? *Acta Oncol* 2010; **49**:278–286.

20 Habr-Gama A, Perez RO, Sabbaga J. Increasing the rates of complete response to neoadjuvant chemoradiotherapy for distal rectal cancer: results of a prospective study using additional chemotherapy during the resting period. *Dis Colon Rectum* 2009; **52**:1927–1934.