Neoadjuvant chemotherapy in MRI-staged high-risk rectal cancer in addition to or as an alternative to preoperative chemoradiation?

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Received 6 September 2011; revised 3 January 2012; accepted 4 January 2012

Background: For patients with resectable rectal cancer chemoradiation (CRT) or short-course preoperative radiotherapy (SCPRT) reduces locoregional failure, without extending disease-free survival (DFS) or overall survival (OS). Compliance to postoperative adjuvant chemotherapy is poor. Neoadjuvant chemotherapy (NACT) offers an alternative strategy.

Methods: A systematic computerised database search identified studies exploring NACT alone or NACT preceding/succeeding radiation. The primary outcome measure was pathological complete response (pCR). Secondary outcome measures included acute toxicity, surgical morbidity, circumferential resection margin, locoregional failure, DFS and OS.

Results: Four case reports, 12 phase I/II studies, 4 randomised phase II and one randomised phase III study evaluated chemotherapy before CRT. Four prospective studies reviewed chemotherapy after CRT. Three phase II studies investigated chemotherapy using FOLFOX plus bevacizumab without radiotherapy. In 24 studies of 1271 patients, pCR varied from 7% to 36%, but with no impact on metastatic disease.

Conclusions: NACT before CRT delivers does not compromise CRT but has not increased pCR rates, R0 resection rate, improved DFS or reduced metastases. NACT following CRT is an interesting strategy, and the utility of NACT alone could be explored compared with SCPRT or CRT in selected patients with rectal cancer where the impact of radiotherapy on DFS and OS is marginal.

Key words: chemoradiation, induction chemotherapy, neoadjuvant, preoperative, radiotherapy, rectal cancer

introduction

Excellent local control has been achieved in rectal cancer with total mesorectal excision (TME) surgery and further improved when preceded by short-course preoperative radiotherapy (SCPRT) [1–4] or chemoradiation (CRT) [5–7]. Meta-analyses of preoperative radiotherapy (RT) for resectable rectal cancer [8, 9] as well as individual trials of SCPRT [3, 4, 10] demonstrate improved local control compared with surgery alone but have shown conflicting effects on overall survival (OS).

Optimal quality-controlled surgery for patients with operable rectal cancer is associated with local recurrence (LR) rates of 8% [11]. However, despite the reassuring results of randomised trials [5], concerns remain that RT increases surgical morbidity [12–14], which can compromise the delivery of postoperative adjuvant chemotherapy. There are also significant late effects [9, 15] and a risk of second malignancies [16].

Magnetic resonance imaging (MRI) allows accurate prediction of mesorectal surgical margin involvement by tumour [17] and of extramural vascular invasion (EMVI) [18]. Two recent studies confirm the ability of preoperative MRI staging to select patients with a low risk of LR when treated with primary surgery alone [19, 20], suggesting a selective policy for preoperative CRT is possible [21].

In metastatic disease, the addition of oxaliplatin to the combination of 5-fluorouracil (5-FU) and folinic acid (FA) (FOLFOX) offers response rates in the range of 50% [22]. Bevacizumab added to standard cytotoxic chemotherapy is associated with improved survival and higher pathologic response rates in patients undergoing resection of colorectal liver metastases [23] but may not affect RECIST-defined response rates [24]. Bevacizumab may be safely administered in the preoperative setting [25], without increasing postsurgical complications [26, 27].

In stage II–III colon cancer patients, adjuvant oxaliplatin significantly improves 3-year disease-free survival (DFS) compared with 5-FU/FA alone [28–31]. However, rectal cancers have usually been excluded from adjuvant studies, and the evidence base for adjuvant chemotherapy after RT is more tenuous [6, 32, 33].
In addition, compliance is a problem since at least 20%–25% of patients in whom chemotherapy with 5-FU might be considered may not be sufficiently fit or decline treatment [5–7]. Compliance to additional postoperative oxaliplatin appears even worse [34].

However, apart from the fluoropyrimidines, cytotoxic agents have not been integrated, at full systemic doses, into concurrent CRT schedules because of overlapping toxicities. As an alternative setting to concurrent CRT (which only delivers 5–6 weeks of chemotherapy) either an induction component of 6–12 weeks of neoadjuvant chemotherapy (NACT) before RT or CRT [35–38], adding chemotherapy after SCPRT or CRT defined as consolidation chemotherapy, which utilises the ‘dead space’ of the interval between the end of CRT and surgery [39, 40] or delivering chemotherapy alone without any RT are potential options [41, 42].

The theoretical advantages/disadvantages of NACT as induction before CRT or SCPRT are summarised in Table 1. Part of the background to the different approaches reflects cultural and historical preferences for CRT or SCPRT, which is really beyond the scope of this article. Response to induction chemotherapy may predict response to subsequent RT (and vice versa). The original hypothesis in the 1980s suggested that induction chemotherapy would reduce the gross tumour burden and improve oxygenation and hence sensitis to radiation or CRT. There are several potential rationales to induction versus consolidation chemotherapy—albeit delivering chemotherapy early on at systemic doses, when high compliance is achieved, is the main aim. These strategies may also impact on the primary tumour, leading to improved locoregional control [6]. Induction chemotherapy before CRT or surgery has an established role in head and neck and oesophago-gastric cancer [43, 44] to facilitate a curative surgical resection or increase the chance of organ-sparing procedures and has proved a popular strategy in rectal cancer.

Consensus recommendations and current National Institute of Clinical Excellence (NICE) clinical guidelines for the diagnosis and management of colorectal cancer have set neoadjuvant treatment strategies as a priority of future research in rectal cancer [45], http://guidance.nice.org.uk/CG131 (19 December 2011, date last accessed). So can preoperative chemotherapy alone be given in full systemic doses, and RT omitted for patients with a high risk of systemic relapse?

This systematic review aims to examine current evidence regarding the potential role of NACT alone or as either induction or consolidation in addition to RT and CRT in rectal cancer.

### methods

A literature search was performed using Pubmed, Embase and Cochrane databases 1990–2011 supplemented by hand-searching of abstracts from the American Society of Clinical Oncology and other international meetings (ESMO, ASTRO). The studies qualified for this review if they met the following criteria: (i) inclusion of patients with primary rectal adenocarcinoma; (ii) neoadjuvant as induction chemotherapy (intravenous or oral) was administered before, and separately from, CRT; (iii) chemotherapy following radiation or CRT (defined as consolidation) was administered or (iv) NACT was administered without any radiation and (v) histopathological results/early end points were provided. Studies were assessed for relevance by RG-J and MKH. The main focus has been on trials in which NACT alone had been delivered. Other randomised, and unrandomised, CRT trials in rectal cancer, which did not utilise chemotherapy alone, were searched for comparison and discussion purposes.

### study quality assessment

We assessed the quality of studies based on the following criteria: whether the study reported inclusion and exclusion criteria; prospectively collected data; clinical stage and imaging modality; follow-up time; and whether toxicity of chemotherapy and CRT were reported separately and data on surgical complications.

Phase II trials rarely report long-term outcome, so we chose pathological complete response (pCR), defined as the inability to demonstrate any viable cancer cells within the operative specimen—according to the methodology of Quirke [46] as the primary outcome measure of efficacy. The pCR rate is defined as the number of patients achieving pCR with the denominator the total number of patients on an intention to treat basis. Complete pathological response is an attractive end point, although this may not be a surrogate for OS [47]. Secondary outcome measures included acute toxicity, surgical morbidity, a negative circumferential resection margin (CRM), node positivity after surgery, LR, DFS and OS.

<table>
<thead>
<tr>
<th>Advantages of neoadjuvant chemotherapy</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early treatment of micrometastases</td>
<td>May delay definitive CRT treatment</td>
</tr>
<tr>
<td>Delivery of chemotherapy at full systemic doses</td>
<td>May reduce compliance to CRT</td>
</tr>
<tr>
<td>Easier to assess clinical response</td>
<td>No evidence of improvement in pathological response (pCR, ypTo-T2N0)</td>
</tr>
<tr>
<td>Response may be better in primary tumour</td>
<td>May cause more surgical morbidity</td>
</tr>
<tr>
<td>Better compliance to neoadjuvant chemotherapy than postoperative</td>
<td>May select radioresistant clones</td>
</tr>
<tr>
<td>May enhance oxygenation/radioresponse</td>
<td>May allow distant/sanctuary site seeding</td>
</tr>
<tr>
<td>May facilitate radical CRT if shrinks</td>
<td>Potential for organ sparing if downstaged</td>
</tr>
<tr>
<td>Potential for curative resection if downstaged</td>
<td>Uncertain effect on local control if RT or CRT not given</td>
</tr>
<tr>
<td>Response to chemo predictive of response to CRT?</td>
<td>May overtreat some good prognosis patients</td>
</tr>
<tr>
<td>Response may define good/bad prognostic groups</td>
<td>Improves overall survival?</td>
</tr>
<tr>
<td>Improves overall survival?</td>
<td>No evidence that NACT offers better DFS over postoperative adjuvant</td>
</tr>
</tbody>
</table>

CRT, chemoradiation; NACT, neoadjuvant chemotherapy; DFS, disease-free survival.
results

Of the 897 abstracts retrieved, 450 that concerned tumours other than rectal adenocarcinoma and 168 non-English publications were excluded.

Publications retrieved were reviewed for those specifically addressing the use of NACT separate from RT in locally advanced rectal cancer and 25/271 which appeared irrelevant and duplications of the same dataset were omitted. The most recent reference or that which provided the most detailed data was selected. This culminated in 242 abstracts for evaluation and a further 214/242, where the chemotherapy was only delivered concurrently with radiation, were excluded. Thus, 28 publications/abstracts, where NACT had been incorporated into CRT regimens either as induction, or consolidation, or as a sole modality before rectal cancer surgery were selected for data extraction and analysis (see Figure 1). To reduce publication bias, both published and unpublished studies were included. Full text copies of all studies were obtained and relevant data independently extracted by two investigators.

Four were case reports [48–51]. Of the 24 studies remaining, 15 have been published as full papers and 9 as published abstracts. There were 16 studies of induction before CRT—11 phase I/II studies [35, 37, 45, 52–60], 4 randomised phase II [36, 61–64] and a single randomised phase III trial [65]. There were 5 studies of consolidation chemotherapy after CRT (Table 2) [38, 39, 66, 67] and 3 feasibility/retrospective studies of NACT alone without radiation (Table 3) [40, 41, 68] making a total of 24 studies and 1271 patients. There were no meta-analyses. We found six previous reviews, none of which appeared to be systematic reviews [69–74].

From personal contacts and searching websites such as www.clinicaltrials.gov, we found several planned or ongoing NACT for rectal cancer studies (GEMCAD, RAPIDO, BACCHUS, COPERNICUS).

### Table 2. Neoadjuvant consolidation chemotherapy following CRT in rectal cancer and before surgery

<table>
<thead>
<tr>
<th>Case Report</th>
<th>No. of patients</th>
<th>Radiotherapy</th>
<th>Chemotherapy</th>
<th>CCR</th>
<th>pCR</th>
<th>R0</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Habr-Gama [39]</td>
<td>34</td>
<td>Yes, 50.4 Gy/28 fractions</td>
<td>FUFA six cycles of FUFA every 21 days (3 with CRT)</td>
<td>14/34 (41%)</td>
<td>5/34 (15%)</td>
<td>No data</td>
<td></td>
</tr>
<tr>
<td>Zampino [40]</td>
<td>50</td>
<td>Yes, 50.4 Gy/28 fractions</td>
<td>Capcitabine 1250 mg/m² × two cycles over 6 weeks</td>
<td>n/a</td>
<td>9/50 (18%)</td>
<td>100%</td>
<td>5-year DFS 85.4%</td>
</tr>
<tr>
<td>Liang [66]</td>
<td>28</td>
<td>45 Gy/25 fractions/33 days</td>
<td>FOLFOX + bevacizumab × six cycles during and after CRT</td>
<td>n/a</td>
<td>7/28 (25%)</td>
<td>100%</td>
<td>Single local recurrence mean 22/12 follow-up</td>
</tr>
<tr>
<td>Garcia-Aguilar [67]</td>
<td>70/74</td>
<td>45 Gy/25 fractions/33 days</td>
<td>Immediate surgery mFOLFOX-6</td>
<td>n/a</td>
<td>11/60 (18%)</td>
<td>No data</td>
<td>No data</td>
</tr>
</tbody>
</table>

CRT, chemoradiation; CCR, complete clinical response; pCR, pathological complete response; n/a, not applicable.

Table 3. Studies of neoadjuvant chemotherapy without radiation

<table>
<thead>
<tr>
<th>Case Report</th>
<th>No. of patients</th>
<th>Eligibility</th>
<th>Induction chemotherapy</th>
<th>Toxicity</th>
<th>pCRb</th>
<th>T Micc</th>
<th>R0</th>
<th>Late outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ishii [68]</td>
<td>26</td>
<td>T3/T4 N0-2</td>
<td>Irinotecan (80 mg/m²), FUFA days 1, 8, and 15 for 4 weeks</td>
<td>Not stated</td>
<td>1/15 (7%)</td>
<td>Not stated</td>
<td>Not stated</td>
<td>5-year RFS 74%, OS 84%</td>
</tr>
<tr>
<td>Schrag [42]</td>
<td>31</td>
<td>Clinical stages II–III (not T4)</td>
<td>FOLFOX-bevacizumab (six cycles bev 1–4)</td>
<td>Two patients withdrawn (angina arrhythmia)</td>
<td>8/29 (27%)</td>
<td>Not stated</td>
<td>29/29 (100%)</td>
<td>No data</td>
</tr>
<tr>
<td>Cernek [41]</td>
<td>20</td>
<td>RT contraindicated or synchronous metastases</td>
<td>Six patients FOLFOX, 14 patients FOLFOX + Bev</td>
<td>Not stated</td>
<td>7/20 (35%) 2/6 (33%) rectal cancer without metastases</td>
<td>Not stated</td>
<td>Not stated</td>
<td>No data</td>
</tr>
</tbody>
</table>

pCR, pathological complete response; RT, radiotherapy; RFS, relapse free survival.
bNumber entering study.
cNumber having had surgery.

*aUsing regression grading not yp.*
The chemotherapy regimens in 15 studies employed the same two cytotoxic agents (a fluoropyrimidine and oxaliplatin), and schedules are very similar (9 studies used XELOX, 5 studies FOLFOX and 1 used the Nordic FLOX regimen), but only 4 studies gave a potentially systemically effective schedule of 3 months [35, 54, 61, 64]. Five studies added additional bevacizumab [37, 40, 41, 63, 66] and one cetuximab [64]. Two further studies used irinotecan, and one each used mitomycin C (MMC)-based [52] and pemetrexed [60] induction chemotherapy, respectively. The randomised phase III trial used 5-FU and FA.

**Response**

Induction chemotherapy has been reported to achieve high downstaging and pCR rates [53], excellent rates of symptomatic improvement (65%) [52], and can be delivered without apparently compromising compliance with CRT. In this study, clinical tumour response was measured using computed tomography and MRI scans, which were repeated after the initial induction chemotherapy component at 12 weeks, and assessed independently by a radiologist blinded to the pathological findings. Clinical response rates with induction chemotherapy varied from 28% [52] and 41% [38] to 59% [64] when cetuximab was added—with no patients observed to have progressive disease. A small study of 10 patients [58] showed that all patients responded to induction chemotherapy treatment before CRT on MRI criteria. Clinical response rates (which varied from 82% to 100%) suggest that induction chemotherapy improved these rates.

The EXPERT phase II study of 78 patients compared a 12-week induction phase of capecitabine and oxaliplatin followed by CRT with capecitabine with CRT alone (total dose 54 Gy) in locally advanced rectal cancer [45]. This phase II study used MRI defined entry criteria and detailed histopathological information on the circumferential resection margin. The radiological response rate to induction chemotherapy, before CRT, was 81% (2 complete and 50 partial radiological responses). The early outcome results of this study appeared impressive, but it is not possible to determine the relative contributions of the induction chemotherapy and the concurrent CRT schedule or the high dose of pelvic RT (54 Gy), as when compared with the group's subsequent study with an identical chemotherapy schedule, but a lower RT dose of 50.4 Gy, the pCR fell from 23% [35] to 14% [64].

A Danish study used two cycles of thrice weekly capecitabine 1000 mg/m² twice daily and oxaliplatin 130 mg/m² in 85 patients defined by MRI as unresectable T3 or T4 [57]. No progression was observed in any of the patients. Induction chemotherapy was followed by preoperative CRT with capecitabine 1650 mg/m² in two divided daily doses combined with 54 Gy in 27 fractions over 5.5 weeks. Overall, 77 patients were assessable for pathological response. Of these, 18 achieved a pCR and 74 underwent an R0 resection.

The AVACROSS study selected patients according to MRI criteria and used four cycles of induction chemotherapy using capecitabine, oxaliplatin and bevacizumab, followed by CRT with capecitabine and bevacizumab [75]. Results are impressive with 98% having an R0 resection and 36% achieved a pCR. Induction systemic chemotherapy using two cycles of irinotecan, 5-FU and leucovorin (LV) over 8 weeks, with irinotecan (80 mg/m²), 5-FU (500 mg/m²) and LV (250 mg/m²) on days 1, 8 and 15 showed that despite a short interval of only 2–4 weeks after the completion of chemotherapy before surgical resection, downstaging was observed in 15 and a pCR in one patient [68].

Two studies from the Memorial Sloan-Kettering Cancer Center support the feasibility of NACT alone in rectal cancer [40, 41]. A retrospective study included 14 patients with synchronous metastatic colon or rectal cancer treated with neoadjuvant FOLFOX ± bevacizumab without radiation followed by resection of the primary and 6 patients with stage II/III rectal cancer without metastases who received pre-op FOLFOX without RT. This study demonstrated an overall pCR rate of 7/20 (35%) and 2/6 rectal cancer patients (33%) without metastases [40].

A feasibility study tested a NACT approach in patients with clinical stage II–III rectal cancer (but not T4 tumours), who were considered candidates for sphincter-sparing surgery [41]. The primary outcome was the R0 resection rate. The treatment regimen combined FOLFOX (oxaliplatin and 5-FU) with most popular method of integrating chemotherapy is the induction before CRT. The pCR with a protracted venous infusion of 5-FU/MMC was 3% [52] but did not appear to increase when 5-FU/capecitabine was partnered with oxaliplatin or irinotecan before CRT and varied from 10% to 31%. Nor did the eight studies reporting CRM positivity or R0 rates (which varied from 82% to 100%) suggest that induction chemotherapy improved these rates.

The pCR rates from phase II, randomised phase II and phase III trials are shown in Table 1 and supplemental Tables S1 and S2 (available at Annals of Oncology online), respectively. The

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**Figure 1.** Literature search process.
bevacizumab, without preoperative radiation, and reported a pCR in 8/29 patients (27%).

**DFS and OS**

Late outcome in terms of DFS or OS were available for only five studies [35, 39, 64, 65, 68]. The EXPERT series published mature results in 105 patients [35] and demonstrated 3-year progression-free survival and OS of 68% (95% confidence interval (CI) 59% to 77%) and 83% (CI 76% to 91%), respectively. The 3-year relapse-free survival for the 93 patients, who had a complete resection, was 74% (CI 65% to 83%). In the more recent Expert C study, the group of patients with wild-type Kras, who received capecitabine, oxaliplatin and cetuximab, the OS at 3 years was 96% [64].

In a small series of 26 patients with image-predicted stage T3 or T4, N0-2 non-metastatic resectable rectal cancer [68] with a median follow-up of 75 months (range 8–97 months) documented only three pelvic relapses. The 5-year relapse-free, and overall, survival rates were 74% and 84%, respectively. In the Danish study cited above, with a median follow-up of 27 months, 36-month actuarial OS was 82% [57].

**Acute toxicity**

Acute toxicity appears high and several studies describe up to 5% toxic deaths within 2 months of therapy and before surgery, usually because of vascular, cardiac or thromboembolic events during induction chemotherapy [35, 39, 45, 57, 64]. In some of these phase II studies, the authors do not clearly report the toxicity profiles separately for concomitant CRT and when used as full-dose chemotherapy alone [39]. A recent study with induction FOLFOX and bevacizumab [59] provoked grade 3/4 toxicity during CRT in 19 of 25 patients (76%).

**Surgical morbidity**

In the above study, 9/25 patients (36%) developed postoperative complications [59]. Surgical morbidity in the AVACROSS study [75] appears also prominent since 11/45 (24%) required surgical re-intervention. Surgical morbidity including wound dehiscence, wound infections and stomal necrosis were in the range of 15% to 31% [39], which were higher (31%), compared with other phase II studies with capecitabine [14, 76] but compares with the largest study of 5-FU-based preoperative CRT in T3/T4 rectal cancer [6], where surgical morbidity was 22.8% and mortality 2.4% in >500 patients in the preoperative CRT arm.

However, case-mix may be different. The reported very high R0 resection rates and excellent OS after induction chemotherapy suggest these tumours were early, hence surgical morbidity appears high in relation to these favourable results.

**Randomised phase II studies**

There have been four phase II randomised studies [36, 61, 62, 64]. The multicentre Spanish study (GCR-3 study) compared a conventional schedule of CRT followed by TME and postoperative adjuvant chemotherapy using capecitabine and oxaliplatin, against induction chemotherapy using capecitabine and oxaliplatin followed by CRT and TME [61]. The pCR rate was similar in both arms, 14% versus 13%. Significantly more patients in the postoperative adjuvant arm had grades 3/4 acute toxicity than in the induction arm (54% versus 19%; P = 0.0004, respectively). In the postoperative adjuvant arm, 25% of patients did not begin treatment and only 51% received all four cycles, whereas 100% of patients in the induction arm began treatment and 92% received all four (P = 0.001). The relative dose intensity for both capecitabine and oxaliplatin were significantly higher in the induction arm, with no differences in RT compliance between the two arms (P = 0.001). Despite the high compliance in the induction arm, 3-year DFS was not increased [62].

**Randomised phase III trials**

In the NSABP R03 study, 267 of 900 planned patients were randomised between preoperative induction chemotherapy plus preoperative CRT versus postoperative CRT plus postoperative chemotherapy with 5-FU and FA [65]. Induction chemotherapy comprised 500 mg/m² of 5-FU with FA weekly for 6 weeks before CRT. Following preoperative CRT, 15% of patients achieved a pCR. Five-year locoregional recurrence was 10.7% in each treatment arm (P = 0.693). A significant improvement of 5-year DFS (65% versus 53%, P = 0.011), a non-significant improvement in 5-year OS (75% versus 66%, P = 0.065) was observed for the preoperative arm.

Overall, the phase II induction chemotherapy prior to CRT trials showed a pCR rate of 20% (94/468 operated), which fell to 18% in the randomised phase II (51/286 operated) and only 14% (17/1230) in the only phase III randomised trial.

**Discussion**

There is good quality evidence that preoperative RT reduces LR but there is little impact on OS. This is not completely unexpected as RT is a localised treatment and local control may not prevent systemic failure. Increasingly MRI staging of rectal cancer can predict rectal cancer with a high risk of systemic failure such as predicted EMVI or nodal disease, even in patients where the surgical resection margins are not threatened. The concept of NACT is a potentially beneficial therapy which might have less early and long-term side-effects compared with preoperative RT. Some patients with both locally advanced and at high risk of systemic failure might benefit from both NACT and preoperative RT and the advances in imaging, in particular pelvic MRI has been key in selecting patients with such risk factors.

The phase II studies show consistently high pCR rates compared with the pooled analysis by Hartley [77], but when induction chemotherapy was used before CRT in a randomised phase II study compared with CRT followed by postoperative adjuvant chemotherapy, the pCR rates were almost identical in each arm 13% versus 14%, respectively [61].

These results do not clarify the optimal chemotherapy regimen or schedule. The induction duration has varied from a combination of capecitabine and oxaliplatin administered over 3 months before capecitabine and radiation [35, 54, 64, 75] or a single course over 2 weeks [55].
induction chemotherapy before CRT

These results suggest that induction chemotherapy before CRT is feasible and can be delivered without compromising either the radiation or subsequent surgery. It remains unclear how much this strategy has added to improving outcomes, possibly because the studies have almost invariably used oxaliplatin before CRT rather than a non-cross resistant cytotoxic agent as in head and neck cancer. We have previously highlighted our concerns with this strategic approach [78], which defies the principles of De Ruyscher [79], i.e. the interval from the start of any treatment to the end of radiotherapy (SER) should be as short as possible.

We also have concerns regarding the high rate of toxic deaths. Patients with the more advanced and larger pelvic tumours appear to have a high risk of thromboembolic and cardiac effects [45], although the risks may be less if T4 tumours are excluded [41]. More rigorous selection of patients and the proactive use of low molecular weight heparin may reduce these risks.

Should we have concern for the use of bevacizumab? For patients treated with bevacizumab within the NO16966 and BEAT studies, there were no surgery-related deaths and serious postoperative complications were uncommon, with grade 3/4 bleeding and wound-healing events reported in 0.4% and 1.8%, respectively [80]. In liver surgery, the use of Bevacizumab appears safe in the preoperative setting [25–27]. However, some studies comment on blurring of surgical planes and the observation of more fragile blood vessels during surgery [66].

consolidation chemotherapy (NACT following CRT)

Habr-Gama recently reported that extending the duration of the chemotherapy post-CRT increased the complete clinical response rate (cCR) of 48% achieving an overall complete response rate (i.e. including cCR and pCR) of 65% [38]. Others have demonstrated an increased pCR when CRT is followed by two courses of FOLFOX chemotherapy and surgery delayed (pCR 25%) compared with standard surgery at 6 weeks (pCR 16%) [67].

Oral capecitabine [39] or FOLFOX with bevacizumab [66] have been administered both concomitant with, and following CRT, before surgery in locally advanced rectal cancer. However, this chemotherapy may be associated with an increased rate of post-surgical complications which was 31% and 21.4%, respectively, in the above studies.

The use of consolidation chemotherapy is attractive as it does not compromise the delivery of CRT. However, the observed increased pCR rates may simply reflect a good early response and leaving a longer interval for this response to be further expressed. Retrospective data from the Memorial Sloan-Kettering Cancer Center suggest that increasing the interval between CRT and surgery can enhance the rate of pCRs in rectal cancer [81].

CRT may also affect the neutrophil count for prolonged periods, which could influence surgical morbidity [31, 82, 83]. In some studies [81, 84], longer intervals appear to be associated with higher complication rates.

NACT without CRT

The primary tumour may be more sensitive to chemotherapy compared with metastatic lesions [85, 86], although recent studies of NACT in patients with stage IV colorectal cancer, show that liver metastases exhibit a better histological response in terms of tumour regression grading compared with the primary tumours [87].

It has been suggested that there may be an inhibitory effect of the primary tumour on the growth of metastases. Both open and laparoscopic resections are associated with significantly elevated plasma vascular endothelial growth factor levels early after surgery [88] suggesting that surgery could stimulate the growth of residual cancer cells. NACT may achieve better access to malignant cells when the tumour has an intact blood supply, be associated with better compliance to treatment [61] and enable full systemic doses of chemotherapy to be delivered. Systemic doses of chemotherapy can be delivered at an early stage of the diagnosis rather than a delay of up to 18 weeks associated with CRT.

Adjuvant treatment in the postoperative setting has frequently been compromised by delays because of surgical morbidity, slow recovery and healing, poor tolerance and marked dose reductions with patient compliance being ∼50% [5–7]. These studies show 20%, 23% and 25%, respectively, failed to start postoperative 5-FU-based adjuvant chemotherapy.

Combinations of oxaliplatin and irinotecan have been incorporated into first-line palliative chemotherapy regimens in advanced colorectal cancer, and more recently, triplets of chemotherapy [89]. In a randomised trial, 6 months of induction chemotherapy with the three-drug regimen FOLFOXIRI demonstrated statistically significant improvements in response rate, radical surgical resection of metastases and progression-free survival, compared with 6 months of induction chemotherapy with FOLFIRI—showing a 5-year survival rate of 15% versus 8%. Integration of targeted monoclonal antibodies has further increased clinical response rates in metastatic colorectal cancer [42, 90–92]. Effective agents in metastatic colorectal cancer—capecitabine, oxaliplatin, irinotecan, bevacizumab and cetuximab and their combinations, because of their high response rates, are being explored in combination with preoperative RT in the neoadjuvant setting to increase tumour shrinkage before surgery.

trials in progress

A Polish study (NCT00833131) in unresectable rectal cancer addresses the question whether SCPRT (25 Gy in five fractions) followed by consolidation chemotherapy using FOLFOX4 can increase the rate of R0 resection compared with the standard of conventionally fractionated CRT (50.4 Gy total dose in 28 fractions of 1.8 Gy over 5.5 weeks with FULV or capecitabine).

A similar study (RAPIDO) is a collaboration of the Dutch and Swedish study groups and compares CRT followed by delayed surgery and postoperative adjuvant chemotherapy with 5 × 5 Gy SCPRT followed by chemotherapy and then followed by surgery.
The present authors are launching a randomised phase II neoadjuvant study BACCHUS (Bevacizumab and Combination Chemotherapy in Rectal Cancer until Surgery) in resectable rectal cancer where preoperative MRI suggests adverse features such as EMVI, but the CRM is not threatened. RT is not planned unless patients are shown to progress. The study aims to evaluate the efficacy, toxicity and feasibility of FOLFOX/bevacizumab versus FOLFOXIRI/bevacizumab with a primary end point of pCR.

limitations

The limitation of this review is that conclusions are based on only 24 studies and 1271 patients. There were four randomised phase II and only a single phase III trial, which had insufficient numbers. Small studies have considerable heterogeneity since the selection of patients, initial staging, the cytotoxic and biological drugs used in NACT, the regimens, the duration and the dose intensity all vary. In addition, the RT component varied in terms of total dose (45–54 Gy) and fraction size. There is also considerable heterogeneity in terms of treatment strategy (NACT followed by CRT, CRT followed by NACT; NACT alone), and some studies also include metastatic patients. Much of the data is also from abstracts, without the benefit of full peer-review. Hence limited conclusions can be drawn, and it is impossible to suggest an optimal chemotherapy schedule.

conclusion

We believe that RT is an important component of the multimodality treatment of rectal cancer if the CRM is threatened. However, for less advanced cases, the risk of metastatic disease now predominates over the risk of LR. The risk of LR is very low if the CRM is not threatened. Modern MRI also can define patients with a high risk of metastases (EMVI, T3c and T3d).

The use of chemotherapy at systemically effective doses therefore seems essential to improve survival in patients with locally advanced rectal cancer. Concurrent, induction and consolidation chemotherapy before surgery are all potential novel strategies for improving outcome.

NACT allows full delivery of chemotherapy in systemic doses and an appropriate intensity without compromising surgery. However, the addition of NACT as induction to CRT does not appear to increase pCR rate, negative CRM rates or R0 resection rates but may increase treatment-related morbidity and even mortality. To date, oxaliplatin-based induction chemotherapy has not improved DFS compared with postoperative adjuvant chemotherapy. Yet, there is now enough preliminary evidence to support the view that in less locally advanced patients selected by initial MRI, the role of NACT alone, without radiation, should be evaluated in a future research programme. However, only well-conducted carefully imaged randomised phase III trials comparing induction chemotherapy, consolidation chemotherapy and chemotherapy alone with the current standard of SCPRT or CRT will provide definitive answers.

funding

No funding was received for the preparation of this article.

disclosures

Dr RG-J has in the past received honoraria for lectures and advisory boards and has been supported in attending international meetings by Merck-Serono, Pfizer, Sanofi-Aventis and Roche. He has also received unrestricted grants for research from Merck-Serono, Sanofi-Aventis and Roche.

Dr MH has in the past received honoraria for lectures and advisory boards and has been supported in attending international meetings by Merck-Serono, Pfizer, Sanofi-Aventis and Roche.

Dr NA and Mr BM have no relevant conflicts of interest.

The present authors are launching a randomised phase II neoadjuvant study BACCHUS (Bevacizumab and Combination Chemotherapy in Rectal Cancer until Surgery) in resectable rectal cancer where preoperative MRI suggests adverse features such as EMVI, but the CRM is not threatened.

references


mTOR inhibitors in the management of hormone receptor-positive breast cancer: the latest evidence and future directions

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Background: There is an unmet therapeutic need in endocrine-resistant, hormone receptor (HR)-positive, human epidermal growth factor receptor 2-negative advanced breast cancer (BC). Preclinical studies support the hypothesis that the mammalian target of rapamycin (mTOR) inhibition could potentially overcome resistance to endocrine therapy.

Materials and methods: A literature review regarding BC and mTOR inhibitors was undertaken. The reference lists from retrieved manuscripts were reviewed to identify further studies.

Results: Phase II studies have reported that the combination of mTOR inhibitors with endocrine therapy shows efficacy in patients with advanced disease that progressed after treatment with aromatase inhibitors. The recent findings of the phase III BOLERO-2 confirmed that everolimus in combination with exemestane significantly improved progression-free survival and response rate, with a manageable safety profile.

Conclusions: The addition of everolimus to exemestane for women with HR-positive metastatic BC is now considered a new therapeutic strategy. However, a word of caution should be added regarding toxic effects, which might limit practical use and compliance. It is essential that clinicians are educated about key recommendations for toxicity management and specific guideline dose modifications. Additional research efforts with the addition of these compounds in the early-stage setting is greatly needed to improve the survival of patients with HR-positive BC.

Key words: breast cancer, endocrine resistance, everolimus, mTOR inhibitors, temsirolimus

introduction

Approximately three quarters of all invasive breast tumors are estrogen receptor (ER)- and/or progesterone receptor (PR)-positive, including at least half of all cancers in premenopausal women [1]. The natural history of hormone receptor (HR)-positive disease differs from that of HR-negative disease in terms of time to recurrence, site of recurrence, and overall aggressiveness of the disease. Compared with patients with ER-negative tumors, patients with ER-positive tumors experience a relatively constant hazard of recurrence over time [2, 3]. In women treated with tamoxifen for 5 years, more than half of all recurrences occur in years 6–15 after diagnosis [4]. Although tamoxifen and aromatase inhibitors (AI) lower the risk of recurrence for several years after they are stopped, late recurrences and deaths remain a major clinical challenge. In the metastatic setting, there are some patients with HR-positive disease who have durable response to antiestrogen therapy, although the majority of patients will have a short survival of <3 years. This review will focus on the management of HR-positive breast cancer (BC), the current standard of care, and the new evidence on use of mammalian target of rapamycin (mTOR) inhibitors in this setting.