Neoadjuvant chemoradiotherapy in rectal cancer

Are there new drug combinations on the horizon?

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Summary Neoadjuvant chemoradiotherapy is a well-established standard treatment for locally advanced rectal cancer and has led to a remarkable improvement in local control. However, distant recurrences still pose a notable threat and local failure, albeit increasingly rare, can lead to unfavorable clinical situations. In this short review, we discuss three promising new strategies to improve rectal cancer treatment: total neoadjuvant therapy, short course radiotherapy, and immune checkpoint inhibitors.

Keywords Colorectal carcinoma · Short-course radiotherapy · Immune-checkpoint inhibitors · Total neoadjuvant therapy · Perioperative treatment

Introduction

Combined-modality therapy (CMT) consisting of surgery, radiation therapy, and chemotherapy still remains the standard treatment for stage II (T3/4 N0 M0) and III (N+M0) rectal cancer. Using this approach, the high rate of local recurrences after sole surgery has been markedly improved. Several studies have investigated the optimal array of the constituents of CMT. Today, the sequence of neoadjuvant chemoradiotherapy or short-course radiation followed by surgery (total mesorectal excision, TME) and, if necessary, adjuvant chemotherapy is most widely used. As a result, distant metastases have superseded local recurrences as the major cause of treatment failure [1–3]. Therefore, the focus has shifted

from improving local control to reducing systemic failure.

Total neoadjuvant therapy

Improvements in chemoradiotherapy have led to a significantly improved local control. However, this did not translate into improved disease-specific survival (DSS) or overall survival (OS) with distant metastases being substantially more common than local recurrence. Consequently, efforts have been undertaken to improve systemic therapy. Adjuvant chemotherapy after neoadjuvant (chemo)radiotherapy has been extensively studied but results are controversial. There is decent evidence favoring the use of adjuvant chemotherapy. In a Cochrane meta-analysis, Petersen and colleagues found a significant improvement in both disease-free survival (DFS) and OS following adjuvant chemotherapy [4]. Additionally, the CAO/ARO/AIO-04 trial and the ADORE trial, two randomized controlled trials, showed that the addition of oxaliplatin to a 5-fluorouracil (5-FU) based chemotherapy leads to a further improved DFS [5, 6]. For patients with ypN2 status and minimally regressed tumors, oxaliplatin even improved OS. Therefore, adjuvant chemotherapy is currently recommended by several guidelines, at least for high-risk tumors [7, 8]. However, there are also studies that show no improvement in DFS or OS following adjuvant chemotherapy [9–12]. Poor compliance with or delayed start of adjuvant therapy due to postoperative complications and suboptimal chemotherapy regimens may explain these unsatisfactory results [13]. As a consequence, clinical trials have assessed the role of pre- rather than postoperative chemotherapy, commonly referred to as total neoadjuvant therapy (TNT) [14]. Several advantages have been attributed to TNT, including early systemic treatment to address

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micrometastases, improved response rates, enhanced R0 resection rates, decreased toxicity, earlier reversal of diverting ileostomy, and the possibility to better select patients for a potential watch-and-wait strategy [6, 15]. TNT usually consists of an oxaliplatin-containing polychemotherapy, such as FOLFOX (folinic acid, fluorouracil, oxaliplatin), CAPOX (capecitabine, oxaliplatin), or FLOX (fluorouracil, oxaliplatin). While there is no level-I evidence regarding the comparison of TNT with neoadjuvant chemoradiotherapy and adjuvant chemotherapy, there is an increasing body of level-II evidence that suggests that TNT is a viable alternative. For instance, in a recently published retrospective cohort analysis from the Memorial Sloan Kettering Cancer Center, Cercek and colleagues analyzed 320 patients who received neoadjuvant chemoradiotherapy with planned adjuvant chemotherapy and 308 patients who received oxaliplatin-based TNT [16]. Importantly, more patients in the TNT cohort completed the planned chemotherapy and the complete response (CR) rates (both pathologic CR [pCR] and clinical CR [cCR] for at least 12 months) were higher in this group (36% vs. 21%). Additionally, significantly more patients after TNT received minimally invasive surgery and ileostomy closure was more likely to be performed within 15 weeks postsurgery in the TNT cohort. However, due to the relatively short follow-up, no data on DFS or OS are shown. There is also no data on treatment-related toxicity. Furthermore, a recent meta-analysis by Petrelli and colleagues has evaluated 28 studies with 2688 patients treated with TNT and 891 patients treated with standard neoadjuvant chemoradiotherapy [17]. Although most of the included studies were prospective cohort studies, the authors showed a significant increase in pCR rates and a significantly better OS. Importantly, this meta-analysis did not address the value of adjuvant chemotherapy. Since optimal scheduling of chemotherapy and chemoradiotherapy in TNT is not clear, the German Rectal Cancer Study Group conducted a multicenter, randomized, phase 2 study in which 306 patients were assigned to induction chemotherapy either before or after neoadjuvant chemoradiotherapy. Interestingly, chemoradiotherapy-related toxicity, compliance with chemoradiotherapy, and pCR rates were significantly better when chemotherapy was given after chemoradiotherapy [18]. Therefore, this TNT sequence is currently being tested in an organ preservation phase II trial (CAO/ARO/AIO-16; NCT05361142) and has been selected for additional phase III comparison with standard neoadjuvant chemoradiotherapy (CAO/ARO/AIO-18).

Short-course radiotherapy

Neoadjuvant short-course radiotherapy (SCRT) with 25 Gy delivered in 5 fractions is an accepted alternative to conventional long-course chemoradiotherapy (LCRT) with 45–50 Gy in 1.8–2 Gy per fraction with

concomitant 5-FU-based chemotherapy [7, 8]. Albeit SCRT was introduced more than 20 years ago in the Swedish Rectal Cancer Trial [19], its role in rectal cancer treatment remains controversial and it is not clear which form of neoadjuvant treatment provides better tumor control and long-term outcomes. Two recent meta-analyses have tried to answer this question. Wang and colleagues analyzed 11 trials (5 prospective and 6 retrospective studies) with nearly 2000 patients and additionally performed a trial sequential analysis (TSA) to account for repeated significance testing. The authors conclude that SCRT is as effective as LCRT in terms of OS, DFS and 3-year local control [20]. Similarly, Ma and colleagues found no differences in these parameters [21]. However, in the latter meta-analysis, the authors showed an advantage of LCRT in terms of pCR (OR 0.05, $p < 0.01$), which did not translate into a higher sphincter preservation rate (OR 1.62, $p = 0.25$). In contrast, SCRT was associated with fewer grade 3/4 acute toxicities, while severe late toxicities were equal between the two regimes. Additionally, the recently published Stockholm III trial showed that delaying surgery for 4–8 weeks after SCRT (as compared to 1 week) does not compromise oncological results but significantly reduces postoperative complications and gives an opportunity to optimize patients and plan surgery well in advance [22]. It furthermore allows for administration of a neoadjuvant chemotherapy after SCRT. This approach has been investigated by the Polish Colorectal Study Group. In a randomized phase III trial, this group compared SCRT followed by consolidation chemotherapy (CCT), consisting of three cycles of FOLFOX (5-FU, folinic acid, and oxaliplatin), with LCRT (with 5-FU, leucovorin, and oxaliplatin). Preoperative treatment toxicity was lower in the SCRT with CCT group and R0 resection rates showed a trend towards favoring SCRT with CCT over LCRT ($p = 0.07$) [23]. Interestingly, early benefits for SCRT with CCT in terms of OS did not persist after a longer follow-up and superiority of SCRT with CCT over chemoradiotherapy could not be demonstrated [24]. Similarly, the randomized phase III RAPIDO trial [NCT01558921] compares conventional neoadjuvant LCRT with SCRT followed by six cycles of CPAEOX (capecitabine and oxaliplatin) and subsequent surgery [25]. However, first results are still pending.

New substances

Immunotherapy with immune checkpoint inhibitors (ICI) turned out to be a quantum leap forward in the systemic treatment of various types of cancer, including colorectal carcinoma (CRC) [26]. Utilizing an ICI-based approach response rates were as high as 40% in patients with metastatic CRC with a deficient mismatch repair (MMR) system [27, 28]. However, in MMR proficient mCRC the efficacy of ICI is very low. In this context, RT has been shown to induce the antigen release from tumors with a low neo-antigen bur-

den, such as MMR proficient CRC. This in turn leads to an anti-tumor immune response, mainly driven by CD8⁺ T lymphocytes. Interestingly, neoadjuvant chemoradiotherapy has been shown to induce long-lasting PD-L1 overexpression in patients with rectal cancer, and this upregulation of PD-L1 is associated with a favorable prognosis [29, 30]. Additionally, the combination of ICI and RT has been shown to exhibit synergistic effects in inhibiting tumor growth in animal models of various tumor types and additionally improves local tumor control in nonirradiated secondary tumors, a phenomenon generally termed abscopal effect [31–34]. Several retrospective studies also support the synergistic effect of ICI and chemoradiotherapy in the neoadjuvant setting [30, 35–38]. Taken together, these findings strongly suggest the integration of ICI in the neoadjuvant setting for the management of rectal cancer. There are several clinical trials investigating this combination: the AVANA trial (NCT03854799) is a phase II trial that investigates the addition of avelumab (α -PD-L1) to standard neoadjuvant chemoradiotherapy with the primary endpoint being the pCR rate. Similarly, the R-IMMUNE trial (NCT03127007) aims at evaluating safety and efficacy of atezolizumab (α -PD-L1) combined with neoadjuvant chemoradiotherapy. In contrast, the PEMREC trial (NCT04109755) seeks to evaluate safety and efficacy of neoadjuvant pembrolizumab (α -PD-1) combined with SCRT without chemotherapy. Importantly, while the concomitant use of ICI and radiation therapy in these trials is certainly appealing and backed up by a myriad of preclinical findings [39], this approach is not clinically validated in any tumor type. In contrast, a consolidative strategy with ICI upon radiation is being tested in two phase II trials: the TARZAN trial (NCT04017455) and the CHINOREC trial (NCT04124601). In the former neoadjuvant treatment with atezolizumab and bevacizumab (α -VEGF) following RT is investigated, while in the latter neoadjuvant ipilimumab and nivolumab after chemoradiotherapy is being tested. This sequential approach is more substantially supported by the positive results regarding DFS and OS of the PACIFIC trial [40]. Interestingly however, in this trial of patients with stage III non-small cell lung cancer (NSCLC), patients who received ICI at the latest 14 days after radiation therapy had the highest benefit [41]. First results of trials investigating neoadjuvant ICI and (chemo)radiotherapy are eagerly awaited and will determine whether these treatments will be pursued in phase III trials.

Conclusion

Although the prognosis for patients with rectal cancer is distinctly better than for many other malignant diseases, refinement of rectal cancer therapy is still mandatory. TNT may improve OS, while SCRT could reduce the burden on patients by shortening treatment time without sacrificing oncologic outcomes.

However, one still has to keep in mind that conventional neoadjuvant chemoradiotherapy has been the standard of care for decades which entails a lot of experience with this regime. Regarding new therapeutic options, it will certainly be exciting to see which position ICI will acquire in the treatment of rectal cancer.

Take home message

- Neoadjuvant chemoradiotherapy still remains the standard of care for stage II/III rectal cancer.
- Total neoadjuvant therapy may improve oncologic outcomes and is being investigated in clinical trials.
- Neoadjuvant short-course radiotherapy is an alternative to conventional neoadjuvant long-course chemoradiotherapy.
- Neoadjuvant immune-checkpoint inhibitors are being tested in several clinical trials.

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Conflict of interest C. Arnold, J. Mangesius, R. Jäger, and U. Ganswindt declare that they have no competing interests.

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