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CHAPTER 6
Total Neoadjuvant Therapy (TNT)

This more recently disseminated strategy is treated in a separate chapter as it introduces a new concept. It is to add to the classic objective of reducing local recurrences, the benefit of potentially prolonging survival, introducing systemic treatment among the first therapeutic tools administered, especially to patients at high risk of distant disease.

The first reported experiences began in the United Kingdom, where some studies were carried out with the indication of neoadjuvant ChT prior to concurrently administered CRT. Cunningham and the Royal Marsden Hospital group conducted a phase II study in which they assigned 77 high-risk patients based on HR-MRA findings (T3c-T4 or N2 or threatened CRM, or location at or below the levator ani muscles), to a treatment consisting of 12 weeks of CAPOX, followed by synchronous CRT with capecitabine, TME at 6 weeks, and another 12 weeks of postoperative capecitabine. The radiological response rate was 88%. In addition, 86% of patients had symptomatic responses within an average of 32 days (e. g., little more than a CAPOX cycle). After CRT, the tumor response rate increased to 97%. Three patients remained inoperable. pCR was observed in 16 patients (24%, CI 95% 14-36%), and in another 32 patients (48%), only microscopic tumor foci were found in the surgical specimens. Four deaths occurred during neoadjuvant CAPOX therapy as a consequence of pulmonary embolism, ischemic heart disease, sudden death with a history of chest pain, and neutropenic colitis.[33] In 2010, the same group presented a somewhat broader experience with 105 patients after excluding those with a significant cardiac history. With this inclusion criterion, only one thromboembolic event was reported. There was 20% pCR and the 3-year disease free survival (DFS) for patients with tumor excision was 74%.[37] These results are encouraging from the oncologic point of view and show that some patients could also benefit because symptomatic relief allows them to reach surgery in better clinical condition.

With these antecedents, the strategy known as TNT implies the addition of ChT prior to surgery, associated with a neoadjuvant regimen, which can be both long-course CRT and short-course RT.

The MSKCC group conducted a study that we will describe in detail later, retrospectively comparing TNT with long-course CRT.[29] Patients in the TNT group received higher percentages of the prescribed dose of planned ChT than did those in the CRT group, and the complete response rate was greater.

From this experience, TNT has two different objectives, although both can be present in the same case:

- First, and fundamental, to attack micrometastatic disease in high-risk patients (N +, EMVI +, etc.).
- Second, to increase the response and downstaging in order to preserve the sphincter and even the organ. Although this was expected, is actually a consequence which appears as a finding of the results.

In this strategy, ChT is not administered with criteria or in radiosensitizing doses, but is indicated in therapeutic doses for systemic disease.

Regarding the first objective, the underlying logic is based on the fact that beyond the advances in surgical technique and neoadjuvant therapy, with improvements in LR and postoperative results, there were not identical improvements in long-term survival, since the risk of distant relapse remains as high as 25% in stage II and 40% in stage III. With the traditional adjuvant ChT regimen after neoadjuvant treatment and subsequent surgery, it is estimated that only approximately 50% of patients receive a full dose of ChT. Furthermore, the reality is that they will at best start ChT 5 to 6 months after diagnosis, and complete treatment within about a year. And studies using systemic ChT in conjunction with RT showed no improvement in rates of pCR or DFS, but they did increase toxicity.

Therefore, in patients with locally advanced rectal cancer and high risk of positive resection margin (T4 tumors or tumors with CRM), or in those with low tumors and clearly metastatic nodes is when the strategy known as TNT (e. g., oxaliplatin-based ChT combined with long-course CRT or short-course RT) can be considered, rather than just long-course CRT or short-course RT.

As seen in the MSKCC study, TNT provides several benefits. First, it is associated with greater adherence to ChT due to greater tolerability in the preoperative compared to the postoperative period. But TNT also leads to improved local control and the possibility of considering NOT if a RCC is achieved, even more so if the patient refuses surgery.

In the case of T3N0 tumors of the upper rectum without CRM involvement, or T1-T2 N0 tumors, even with a low

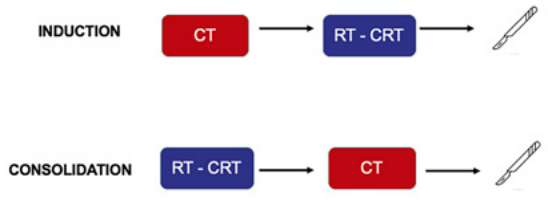

Figure 1: TNT regimens.

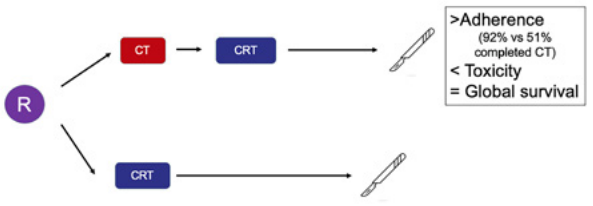

Figure 2: Induction TNT vs. long-course CRT. R = Randomized.

location, TNT is not recommended since these patients will hardly require ChT for the management of their disease, and expose them to this treatment probably involves unnecessary risk. It was also stated that although some trials such as OPRA and PRODIGE 23 included patients with these characteristics, this should not be considered outside of a research protocol.[41,65]

A current discussion is whether TNT should be used in cases with little or no risk of metastatic disease where there will never be an indication for systemic ChT (e. g., T1-3N0 distal tumors without CRM involvement), to avoid a low anastomosis and improve the likelihood of rectal preservation (not just the sphincter). While TNT truly improved organ preservation rates within one year, chemotherapy ChT alone is associated with risk of mortality. In any case, oxaliplatin-based regimens can leave a lasting neuropathy as a sequel without any contribution to cancer control. This is a scenario that no one would want for himself or for any patient.

Finally, in T3N0 tumors of the lower rectum that might require an APR (or a coloanal anastomosis), it seems more reasonable to discuss this option with the patient in order to seek a CCR and preserve the sphincter and the organ.

Variants of TNT

There are still many unanswered questions related to the ChT drug of choice (oxaliplatin, irinotecan or both) and its administration time (3, 4 or 6 months).

There are two different ways of applying TNT, which depend on the way of sequencing the ChT in time (Fig. 1):

- When ChT as part of TNT is given before either long-course or short-course RT, it is called induction ChT or TNT.
- On the contrary, when ChT is applied after RT in any of its 2 forms (short or long-course), it is called consolidation ChT or TNT.

In both cases, the objective is to attack the micro-metastatic disease, but the benefit of increasing resectability and the number of PCRs with both variants has also been demonstrated. This second effect could be due not only to the action of the ChT, but also in the case of the consolidation ChT, the longer time that elapses from the end of the RT to the surgical procedure.

Finally, TNT can be administered in association with long-course RT or short-course CRT. Next, we will evaluate the evidence with all these variants.

TNT + Long-course CRT

Induction QT

We will analyze here three studies that compared induction TNT associated with long-term CRT versus other neoadjuvant alternatives:

- A study published by Fernández Martos in 2010 randomized induction ChT + CRT + TME versus CRT + TME.[54] Although there were no differences in PCR rate or response levels, a lower grade 3-4 toxicity was observed in the first group and a greater number of patients who started (100 vs. 75%) and completed (92 vs. 51%) ChT. However, in a subsequent analysis of the same group of patients after a follow-up of 69.5 months, this greater adherence to CHT did not translate into differences in OS or DFS.[55] (Fig. 2).
- A preliminary report of the phase III study known as PRODIGE 23 was presented at ASCO 2020.[41] In this trial, 461 patients with T3-T4 tumors were randomized to induction ChT with FOLFIRINOX for 3 months (5-FU, oxaliplatin and irinotecan) + CRT + TME + adjuvant ChT for another 3 months vs. CRT + TME + adjuvant ChT for 6 months. Adherence to ChT was 92% in the induction group and 75% in the control group. Furthermore, in the induction ChT group, the PCR was 28 vs. 12%, and the 3-year DFS was 76 vs. 69%, both significant differences (Fig. 3).
- The MSKCC group performed a retrospective analysis of 811 patients with T3-T4 or N + tumors, among whom 320 received CRT followed by surgery and adjuvant ChT and 308 TNT with induction ChT.[29] The patients in the TNT group had greater adherence to ChT and although there were no differences in the PCR rate among the operated patients (18% TNT vs. 17% CRT), when adding the non-operated patients (those who achieved a CCR sustained beyond one year) the percentage rose to 36% in TNT vs. 21%

in CRT. During the period studied (2009-2015) at MSKCC the indication for non-operative treatment (NOT) increased. What was observed is that the number of patients included in this protocol was also higher with TNT (27 vs. 7.5%) (Fig. 4).

In conclusion, induction TNT associated with long-course CRT increases the response, favors adherence to ChT and reduces toxicity, but definitive data on its benefits in terms of survival are still lacking.

Consolidation ChT

We will now analyze three studies that compared consolidation TNT associated with long-course CRT with some form of CRT:

- In 2014, Myerson et al.157 reported the experience in a group of 76 patients with T3-4 tumors, who underwent a short-course RT regimen followed by consolidation ChT with FOLFOX. Ninety-five percent of patients completed the treatment and achieved 25% PCR with only 9% grade 3 toxicity. In a subsequent analysis, this same group of patients was compared with a population treated with CRT and found that TNT allowed obtaining a better DFS (85 vs. 68%) and metastasis-free survival (88 vs. 70%) 142 (Fig. 5).
- García Aguilar et al.,[66] in a multicenter study conducted in the US and Canada, compared CRT followed by surgery vs. CRT followed by 2, 4 or 6 cycles of consolidation ChT with FOLFOX and subsequent surgery. An increase in PCR rates was achieved, which were 18 vs. 25, 30 and 38% respectively. In a subsequent analysis of this same series of patients, a higher rate of PCR and even a better pathological stage (yp) were again demonstrated, and also that the TNT regimen with consolidation ChT with FOLFOX (compared with CRT followed by adjuvant treatment) had better DFS rates with statistically significant values[138] (Fig. 6).
- Chapman et al.[32] compared long-course CRT vs. short course RT + TNT with consolidation ChT vs. long-course CRT + TNT with consolidation ChT. The objective was to compare the NeoAdjuvant Rectal Score (NAR score, to which we will refer later) as a surrogate for OS, showing that both forms of consolidation TNT had a more favorable NAR score than CRT, and that long-course CRT + consolidation was the treatment regimen that obtained the lowest (best) NAR score (Fig. 7).

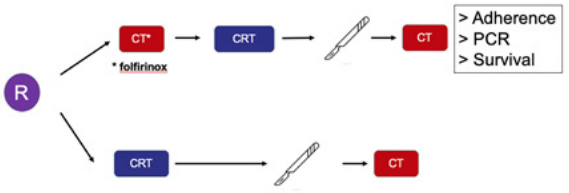

Figure 3: Induction TNT vs. long-course CRT. R = Randomized.

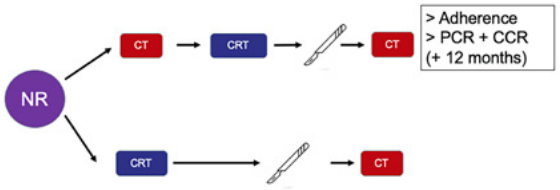

Figure 4: Induction TNT vs. long-course-CRT. NR = Non-randomized.

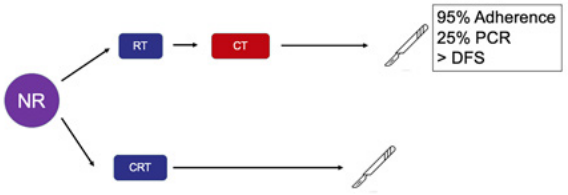

Figure 5: Consolidation TNT vs. long-course CRT. NR = Non-randomized.

These studies seem to show that consolidation TNT associated with long-course CRT, in addition to the benefits of induction TNT, adds some influence to improve DFS rates, although no definitive benefits are demonstrated in terms of OS.

TNT + Short-course RT

The following studies compared TNT associated with short-course RT with traditional neoadjuvant regimens:

- The study known as the Polish II Trial, in a group of 541 patients with fixed T3 and T4 tumors, compared a TNT regimen with consolidation ChT with FOLFOX associated with short-course RT vs. long-course CRT with the addition of oxaliplatin.[39] There were no differences in the rate of complete resections, PCR, or

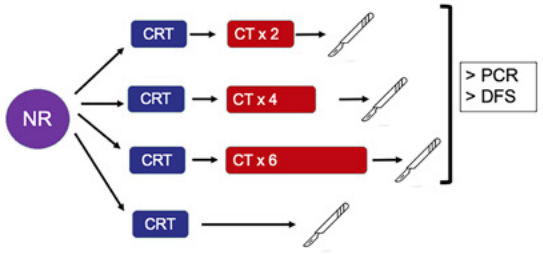

Figure 6: Consolidation TNT vs. long-course CRT. NR = Non-randomized.

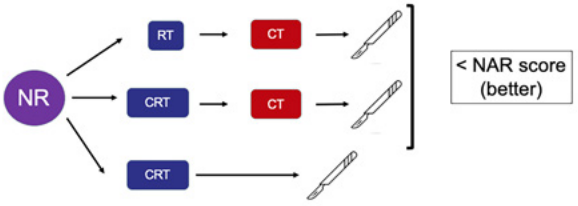

Figure 7: Consolidation TNT vs. long-course CRT. NR = Non-randomized.

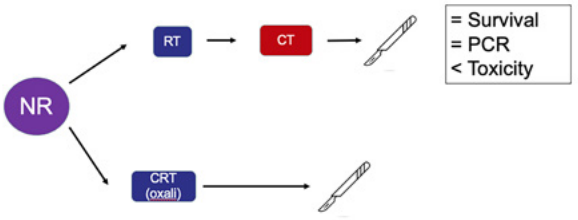

Figure 8: Consolidation TNT vs. long-course CRT. NR = Non-randomized.

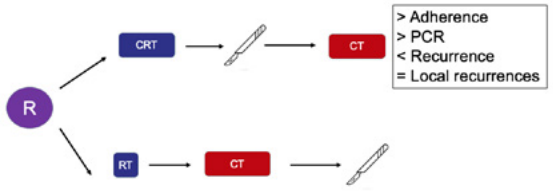

Figure 9: Consolidation TNT with short-course RT vs. long-course CRT. R = Randomized.

8-year survival, and although toxicity was lower in the TNT group with consolidation ChT, the addition of oxaliplatin to CRT regimens has been discussed due to its high toxicity (Fig. 8).

- The RAPIDO study enrolled 920 patients with very high-risk tumors (T4, EMVI +, N2, LNN +, MRC +) and compared short-course RT followed by 18 weeks of consolidation QT with CAPOX or FOLFOX, and subsequent surgery vs. Long-course CRT followed by surgery and adjuvant ChT also based on oxaliplatin.[4,236] Adherence to ChT was 84% in the experimental arm vs. 57% with CRT and, although toxicity was higher, this did not translate into greater postoperative complications. Significant differences were also observed in favor of TNT in the pCR rate (28 vs. 14%), in relapses (24 vs. 30%) and in the appearance of metastases (20 vs. 27%) at 3 years. There were no differences in locoregional relapses (Fig. 9).
- A recent meta-analysis that included several randomized clinical trials showed that TNT increases the rate of pCR but not sphincter preservation and improves DFS but not OS.[112]
- Despite this lack of evidence and the risk of overtreatment posed by TNT, the latest NCCN guidelines include TNT among the various options for patients with T3 tumors with CRM +, T4, or N1-2, and for locally unresectable or medically inoperable patients.

Although studies have shown greater adherence to ChT, the survival benefit remains theoretical, since a difference in its favor has not yet been demonstrated in its favor compared to the classic neoadjuvant regimens with RT or CRT followed by adjuvant ChT.

Induction vs. consolidation

Some studies were conducted that compared induction TNT vs. its variant with consolidation ChT, with the focus on the usefulness of this strategy to achieve organ preservation:

- This issue was addressed in the phase II study known as CAO / ARO / AIO-12.[58] In this trial, it was observed that consolidation TNT would be associated with lower toxicity, greater adherence during RT, and a higher pCR rate than with induction TNT. However, the interval to surgery was 6 weeks in those randomized to consolidation vs. 12 weeks in those who received induction. On the other hand, adherence to ChT was higher with induction and DFS was not analyzed (Fig. 10).
- This question was also addressed in the Organ Preservation of Rectal Adenocarcinoma (OPRA) trial, in which 324 HR-MRI stage II or III patients were randomly assigned to four months of oxaliplatin-ba-

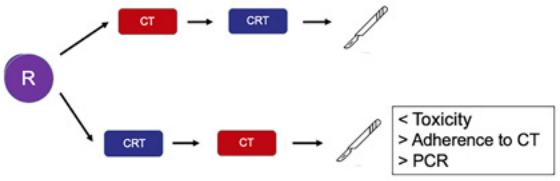

Figure 10: Induction vs. consolidation TNT. R = Randomized.

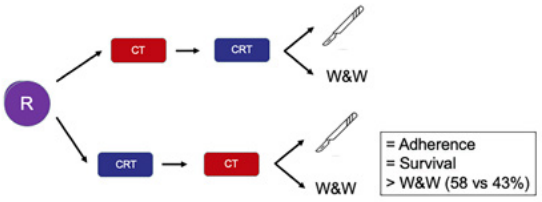

Figure 11: Induction vs. consolidation TNT. R = Randomized.

sed ChT before (induction) or after (consolidation) CRT.[65] After 8 to 12 weeks, they were restaged with digital rectal examination, flexible sigmoideoscopy and HR-MRI, and TNO was offered to those with a complete or almost complete response, while the rest went to TME. After a mean follow-up of 2 years, compliance with systemic ChT was similar in both arms (81 vs. 82%), as was 3-year DFS (77 vs. 78%). However, patients treated with consolidation rather than induction ChT had significantly higher organ preservation rates (58 vs. 43%) (Fig. 11).

These studies show that consolidation ChT allows a response rate even higher than that achieved with induction ChT, which has already been shown to surpass traditional neoadjuvant treatment in this regard.

Conclusions related to TNT

After evaluating all the evidence that arises from the analyzed studies, some conclusions can be drawn:

- When the goal of TNT is to treat micrometastatic disease in high-risk patients, induction CT could be the preferred option to avoid delaying the start of systemic treatment, since no definitive advantages have been demonstrated with consolidation of CT in survival terms.
- When what is sought is only to preserve the organ or the sphincter, the most reasonable thing is to start with RT or CRT, evaluate the clinical response and, if it is evident but not complete, opt for consolidation CT. This will avoid administering and exposing the risk of CT to patients who will probably never require it.
- Short-term RT followed by TNT consolidation has all the advantages, since it practically does not delay the appearance of systemic QT and achieves very high response rates, which is why it appears as an ideal and increasingly considered option.