Session 4: Trying to augment response with chemotherapy: a triumph of hope over experience?

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Abstract

As part of an approach to improve tumour regression and increase the proportion of patients with complete clinical and radiological response, Dr Perez reviews the methods and evidence base for augmenting therapy and thus augmenting response rates preoperatively. Much of the data reviewed were in the context of patients undergoing a watch-and-wait approach for rectal cancer after initial treatment with chemoradiotherapy.

There is much interest in tailoring management based on tumour response to chemoradiotherapy (CRT). At one end of the spectrum, patients who do not achieve a complete response might still need a radical operation; on the other hand, patients who achieve a complete clinical and radiological response may not need an operation at all.

Achieving a complete response is a highly clinically relevant end-point. These patients are known to have an improved oncological outcome [1], so achieving a complete response in an increased proportion of patients has the potential to improve overall survival. Also, a more significant proportion of patients could avoid radical surgery; in itself, this has the potential to result in survival gains [2].

The standard regimen

The standard CRT regimen consists of 50.40 Gy over 6 weeks and two cycles of chemotherapy (concurrent leucovorin (20 mg/m²/day) with bolus doses of 5-fluourouracil administered intravenously at 425 mg/m²/day for three consecutive days) on the first and last 3 days of radiation therapy [3]. This approach achieved a complete response rate of 27.5% [3]. Professor Habr-Gama persuaded the radiation oncologist and medical oncologist at her institution to extend the CRT regimen because she believed a higher response rate was possible.

The extended regimen

In a true episode of wishful thinking 10 years ago, the radiation oncologists came up with three changes:

1. A slight increase in the radiotherapy dose. The total dose was increased from 50.4 Gy to 54 Gy, achieved by nearly doubling the boost dose from 5.4 Gy to 9 Gy [4];
2. An increase in the interval;
3. An increase in the dose of CRT. Instead of the two cycles of chemotherapy on three consecutive days we began to give six cycles on three consecutive days. This is almost as high as the dose given for systemic chemotherapy treatment in Stage II colorectal cancer.

Moreover, in addition to concomitant chemotherapy during the radiotherapy there was also the provision of consolidation chemotherapy during the time that used to be called the ‘resting period’ [5]. Finally, in order to accommodate those three cycles of chemotherapy every 21 days, the interval between CRT and assessment of tumour response was increased, from 8 to 10 weeks. Extending this interval, and taking into account the data suggesting ‘the more you wait the more you gain’ in terms of tumour regression, may have played a role in the improved response rate with the new regimen [6].
The extended regimen: complete clinical response rates

Looking back at the standard regimen with a 27% complete response rate, we came up with a new regimen. The first report, published in 2009, showed a surprisingly high complete clinical response rate of 65% [5] (Fig. 1). However, the series follow-up was too short and the sample size was small. In 2013 we had 70 patients with 53 months of follow-up. The data showed an initial complete response rate of 68%; however, 17% (eight of 47) developed an early regrowth (meaning that recurrence develops in the first year). An additional 10% (four of 39) developed late recurrence after 1 year, resulting in a recurrence rate of 27% for patients with a complete clinical and radiological response [7].

It is important to remember that patients with T2, N0 disease are irradiated if they are otherwise considered for an abdominoperineal excision (APE) [8].

Metabolic activity: standard vs extended CRT regimen

It was also considered if there were any metabolic differences between those patients undergoing standard chemotherapy compared with an extended CRT regimen. Sequential positron emission tomography/computed tomography (PET/CT) imaging was performed in patients undergoing standard and extended CRT regimens, and the maximum standard uptake value (SUV$_\text{max}$) was reviewed.

There is a significant decrease in tumour metabolism between baseline and 6 weeks (as measured using the SUV$_\text{max}$); however, there is no decrease between 6 and 12 weeks [9]. A significant decrease in SUV$_\text{max}$ was an independent predictor of a complete response in our series. There was a cut-off value of 67%, meaning that any patients with $>67\%$ decrease in SUV$_\text{max}$ from baseline were more likely to have a complete response [10]. Therefore, with an average SUV of 63% it is unsurprising that there was only a modest complete response rate (Fig. 2) [9].

If you consider the patients undergoing extended radiotherapy, there is a much greater decrease in the SUV$_\text{max}$ between baseline and 6 weeks, with an average decrease in SUV$_\text{max}$ of 88%, corresponding to an increased rate of complete response (Fig. 2). These differences were statistically significant at both 6 and 12 weeks, implying that there is no recuperation of tumour metabolism [9].

In patients who underwent standard CRT there was increase in SUV$_\text{max}$ between 6 and 12 weeks, but with the extended regimen there was an average decrease in SUV$_\text{max}$ over the same time interval. Therefore, there were more patients with increased SUV$_\text{max}$ in the standard CRT regimen than in the extended CRT regimen (Fig. 2) [11].

Conclusion

With an augmented amount of chemotherapy, doubling the boost and by stretching the interval between completion of CRT and the assessment response, a significant increase in the complete response rate was
demonstrated. In addition, there were decreases in tumour metabolism, with more patients achieving a decrease in the SUV\textsubscript{max} of $>67\%$ and, unlike the SUV\textsubscript{max} outcomes for the standard CRT, this outcome was sustained up to 12 weeks. Finally, the extended regimen avoided the recuperation of tumour metabolism that was previously seen with the standard CRT regimen. Therefore, if you plan to wait more than 6 weeks, it is probably safer to routinely offer patients an extended CRT regimen.

Summary of the key points
- A significant increase in complete response rates has been demonstrated by augmenting the amount of chemotherapy, doubling the boost and extending the interval between completion of chemoradiotherapy and response assessment.
- The extended radiotherapy regime resulted in decreased tumour metabolism with a greater decrease in SUV\textsubscript{max} outcomes when compared with standard chemoradiotherapy, which is sustained up to 12 weeks.
- The extended radiotherapy regime avoids the recuperation of tumour metabolism that has been seen with standard chemoradiotherapy.
- For patients where you plan to wait for more than 6 weeks, an extended chemoradiotherapy regimen is safer.

Conflicts of interest
The authors have no conflicts of interest.

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