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ORIGINAL RESEARCH

Medicine Science International Medical Journal

Medicine Science 2017;6(4):640-2

Is there a relation between the changes in circulating lymphocyte counts due to neoadjuvant chemoradiotherapy and intratumoral lymphocytic response and tumor regression grade in locally advanced rectal cancers?

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Received 11 April 2017; Accepted 20 April 2017
Available online 27.04.2017 with doi: 10.5455/medscience.2017.06.8631

Abstract

There are controversies about the relation between the peripheral lymphocyte levels and response to neoadjuvant therapy. While some authors have reported that a positive correlation between peripheral lymphocyte levels and tumor response, others have suggested the opposite. In the present study, we aimed to investigate the possible relations between the changes in circulating lymphocyte counts due to neoadjuvant chemoradiotherapy (CRT) and intratumoral lymphocytic response (ILR) and tumor regression grade (TRG) in locally advanced rectal cancers. Lymphocyte levels before, during and after CRT as well as before surgery and pathologic findings including ILRs and TRGs were recorded. Lymphocyte levels before CRT were accepted as absolute values. After the changes in the lymphocyte levels during and after CRT and before the surgery were recorded as ratios to the absolute values, the relation between the changes in lymphocyte levels, ILR and TRG were studied by using Pearson and Spearman correlation tests. There was a positive correlation between changes in peripheral lymphocytic levels after neoadjuvant CRT and ILRs. However, there were no other correlations between changes in lymphocytic levels and TRGs and ILRs. The changes in the peripheral lymphocyte counts after CRT may be predictive for ILR. Further studies may provide more information about the relation between peripheral lymphocytes and TILs and tumor response to neoadjuvant CRT.

Keywords: Rectal neoplasms, neoadjuvant therapy, lymphocyte count, intratumoral lymphocytic response, tumor regression grade.

Introduction

The immune system can detect cancer cells as they form by recognizing major histocompatibility complex (MHC) molecule expression [1]. Once activated, T cells migrate to the tumor site and stage effective antitumor immune responses [2]. It has been shown that a reduction in tumor infiltrating T cells (TILs) is associated with recurrence in patients following potentially curative resection for colorectal cancer [3]. In malignancies, higher levels of peripheral lymphocytes are associated with better prognosis, however lymphocytopenia induced by the systemic inflammatory response leads to depression of innate cellular immunity, such as decrease in T4 helper lymphocytes and an increase in T8 suppressor lymphocytes, which may attenuate the tumor-spesific response [4].

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Neoadjuvant therapy reduces local recurrence risk and increase sphincter preservation of advanced rectal cancer. However, there are controversies about the relation between the peripheral lymphocyte levels and response to neoadjuvant therapy. While some authors have reported that a positive correlation between peripheral lymphocyte leves and tumor response, others have suggested the opposite [5,6].

In the present study, we aimed to investigate the possible relations between the circulating lymphocyte numbers before, during and after neoadjuvant chemoradiotherapy and intratumoral lymphocytic response and tumor regression grade in locally advanced rectal cancers.

Material and Methods

We retrospectively analyzed the records of all patients who underwent surgery, either low anterior resection or abdominoperineal resection, due to rectal adenocarcinoma following neoadjuvant chemoradiotherapy (CRT) in Eskisehir

Osmangazi University between January 1, 2014 and May 1, 2016. Patients were staged with abdominopelvic computed tomograpy (CT) and/or pelvic magnetic resonance imaging (MRI) preoperatively and patients with clinically node positive (cN+) or T3/T4 with cN- received neoadjuvant CRT and underwent surgery 8 weeks after CRT completion. Exclusion criteria were unresectable diseases or incomplete data. Basic patient demographics, lymphocyte levels and percentages before, during and after neoadjuvant chemoradiotherapy as well as before surgery and pathologic findings including intratumoral lymphocytic responses (ILR) (no response – mild – moderate – marked) and tumor regression grades (TRG) were recorded (According to the 2010 American Joint Committee on Cancer (AJCC); TRG 0 – no viable cancer cells, TRG 1: moderate response; TRG 2 – minimal response; TRG 3 – poor response) [7,8]. Lymphocyte levels before neoadjuvant therapy were accepted as absolute values.

After the changes in the lymphocyte levels during and after neoadjuvat therapy and before the surgery were recorded as ratios to the absolute values, the relation between the changes in lymphocyte levels, ILR and TRG were studied by using Pearson and Spearman correlation tests. The statistical analysis was performed using SPSS software program version 21 (SPSS Inc., Chicago, IL).

The study protocol was approved by the local ethical committee.

Results

Of 60 patients with rectal adenocarcinoma, 35 were eligible for the study. Seven patients were excluded because they did not receive neoadjuvant CRT due to T1/T2 tumor without radiological lymph node involvement whereas 15 patients were excluded because of insufficient data and 3 patients due to unresectable disease. The mean age of the patients was 61.4 and majority of the patients were male (n=21). In 4 of the patients complete regression was observed (TRG 0) while 10 patients had stage I, 9 patients had stage 2, 10 patients had stage 3 and 4 patients had stage 4 tumors according to TNM staging system. Of the patients, peripheral lymphocyte levels and lymphocyte percentages during and after neoadjuvat therapy and before the surgery, who were categorized according to ILRs and TRGs (Table 1 and 2). Then, the coefficients of the correlations between the changes in lymphocyte levels, ILR and TRG and the statistical significances were expressed in Table 3.

Table 1 . Peripheral lymphocyte levels and lymphocyte percentages in patients who were categorized according to ILRs

		Lymphocyte levels and percentages Mean (SD)			
		Before neoadjuvant CRT	**During neoadjuvant CRT**	**After neoadjuvant CRT**	**Before surgery**
Intratumoral lymphocytic response	**No response (n=4)**	2,47 (0,61) %26,93 (5,75)	1,07 (0,60) %18,57 (12,00)	0,60 (0,17) %12,30 (7,36)	1,17 (0,06) %20,30 (4,90)
	Mild (n=15)	1,66 (0,46) %22,37 (4,18)	0,81 (0,36) %16,19 (5,71)	0,57 (0,30) %11,22 (5,38)	0,86 (0,31) %15,21 (4,81)
	Moderate (n=11)	1,40 (0,48) %19,59 (5,84)	0,69 (0,31) %12,95 (4,98)	0,56 (0,21) %11,16 (4,86)	0,90 (0,32) %16,00 (3,74)
	Marked (n=5)	1,87 (1,33) %21,00 (6,21)	1,23 (0,60) %16,53 (6,82)	0,83 (0,06) %10,67 (1,21)	0,87 (0,12) %16,07 (3,55)

SD:standard deviation, CRT: chemoradiotherapy

Table 2 . Peripheral lymphocyte levels and lymphocyte percentages in patients who were categorized according to TRGs

		Lymphocyte levels and percentages Mean (SD)			
		Before neoadjuvant CRT	**During neoadjuvant CRT**	**After neoadjuvant CRT**	**Before surgery**
Tumor regression grade	**Grade 0 (n=4)**	1,23 (0,43) %20,10 (4,74)	0,98 (1,03) %16,85 (13,28)	0,50 (0,16) %10,13 (2,49)	0,83 (0,17) %17,83 (2,60)
	Grade 1 (n=9)	1,70 (0,53) %25,82 (4,36)	0,95 (0,52) %16,59 (6,65)	0,48 (0,27) %11,05 (6,25)	0,79 (0,30) %17,75 (3,64)
	Grade 2 (n=17)	1,72 (0,69) %22,34 (4,69)	0,92 (0,38) %16,49 (5,58)	0,69 (0,24) %12,79 (4,92)	0,93 (0,32) %16,18 (5,12)
	Grade 3 (n=5)	1,93 (0,32) %23,53 (4,00)	0,57 (0,12) %11,80 (9,32)	0,37 (0,12) %6,50 (2,38)	0,97 (0,21) %18,40 (3,15)

SD:standard deviation, CRT: chemoradiotherapy

Table 3 . The correlations between the changes in lymphocyte levels, ILR and TRG

		Ratio of lymphocyte levels to the levels before CRT		
		During neoadjuvant CRT	**After neoadjuvant CRT**	**Before surgery**
Intratumoral lymphocytic response	**Pearson correlation**	0,279	0,375	0,152
	P	0,143	0,045	0,432
Tumor regression grade	**Spearman correlation**	-0,149	-0,019	0,019
	P	0,393	0,916	0,914

CRT: chemoradiotherapy

Discussion

In the present study, we have observed that there was a positive correlation between changes in peripheral lymphocytic levels after neoadjuvant CRT and TRGs and ILRs. However, there were no other correlations between changes in lymphocytic levels and TRGs and ILRs.

The correlation between the change in peripheral lymphocyte levels due to neoadjuvant therapy and TRG and ILR in locally advanced rectal cancers has not been thoroughly investigated. Kitayama et al have proposed in a short report that peripheral lymphocyte number has a positive association with tumor response in neoadjuvant chemoradiotherapy for advanced rectal cancer [5]. On the other hand, Ishihara et al indicated that radiation-induced apoptosis of peripheral blood lymphocytes may be predictive for histological regression of rectal cancer in response to preoperative chemoradiotheapy [6]. However, in a more recent study, Polli and Pinho reported that they could not demonstrated a significant relationship between complete tumor response and peripheral leukocyte parameters [9]. In our study, we have observed a marked reduction in the peripheral lymphocyte count as Ishihara emphasized due to radiation-induced apoptosis after CRT.

In previous studies, it has been reported that TILs are associated with better prognosis in colorectal cancer patients [3,10]. Teng et al showed that high pretreatment levels of CD3+ and CD8+ TILs were associated with good response to CRT [11]. Since primed T cells exert their function by infiltration through post-capillary venules into the target tissues [12], we proposed that ILR may be relevant to the peripheral lymphocyte levels. We observed that lymphocyte counts are reduced by CRT in all patients whereas greater ILRs in patients with relatively higher levels of peripheral lymphocytes after CRT. However, we did not find any relation between the peripheral lymphocyte counts and TRGs.

The major limitation of this study was the small sample size. Another limitation was that we did not have the chance to evaluate the percentages of cytotoxic T lymphocytes in the total lymphocyte count and to compare with the numbers of cytotoxic T lymphocytes in tumors.

Conclusion

As a result, the changes in the peripheral lymphocyte counts after CRT may be predictive for ILR. Further studies may provide more information about the relation between peripheral lymphocytes and TILs and tumor response to neoadjuvant CRT.

The authors declare that there are no conflicts of interest and there has been no financial support for this work.

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