Radiotherapy and Oncology xxx (2018) xxx–xxx

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Original article

High lymphocyte count during neoadjuvant chemoradiotherapy is associated with improved pathologic complete response in esophageal cancer

Penny Fang [a], Wen Jiang [a], Rajayogesh Davuluri [c], Cai Xu [a], Sunil Krishnan [a], Radhe Mohan [b], Albert C. Koong [a], Charles C. Hsu [c,*], Steven H. Lin [a,*]

[a] Department of Radiation Oncology, The University of Texas MD Anderson Cancer Center; [b] Radiation Physics, The University of Texas MD Anderson Cancer Center, Houston; and [c] Department of Radiation Oncology, The University of Arizona, Tucson, United States

ARTICLE INFO

Article history:
Received 1 October 2017
Received in revised form 17 February 2018
Accepted 22 February 2018
Available online xxxx

Keywords:
Absolute lymphocyte count
Lymphopenia
Chemoradiation
Pathologic response
Esophageal cancer
Neoadjuvant

ABSTRACT

Background and purpose: Neoadjuvant chemoradiation (nCRT) can reduce tumor infiltrating lymphocytes. We examined absolute lymphocyte count (ALC) nadir during nCRT for esophageal cancer (EC) and pathologic complete response (pCR).

Materials and methods: Patients with stage I–IVA EC ($n = 313$) treated 2007–2013 with nCRT followed by surgery were analyzed. ALC was obtained before, during/weekly, and one month after CRT. pCR was defined as no viable tumor cells at surgery. High ALC was defined as nadir of $\geq 0.35 \times 10^3/\mu L$ (highest tertile). Comparison of continuous and categorical variables by pCR was assessed by ANOVA and Pearson's chi-square. Univariate/multivariate logistic regression was used to assess predictors of pCR and high ALC nadir.

Results: Eighty-nine patients (27.8%) achieved a complete pathological response (pCR). For patients with pCR, median ALC nadir was significantly higher than those without ($0.35 \times 10^3/\mu L$ vs $0.29 \times 10^3/\mu L$, $p = 0.007$). Patients maintaining high ALC nadir had a higher pCR rate (OR1.82, 95%CI 1.08–3.05, $p = 0.024$). Predictors of high ALC included treatment with proton therapy vs. IMRT (OR4.18, 95%CI 2.34–7.47, $p < 0.001$), smoking at diagnosis (OR2.80, 95%CI 1.49–5.25, $p = 0.001$), early stage I–II disease (OR2.33, 95%CI 1.32–4.17, $p = 0.005$), and SCC histology (OR3.70, 95%CI 1.01–14.29, $p = 0.048$). Mean body dose (MBD) was inversely related to high ALC nadir (OR0.77 per Gy, 95%CI 0.70–0.84, $p < 0.001$).

Conclusion: A higher ALC level during nCRT is associated with a higher rate of pCR for esophageal cancer patients undergoing trimodality therapy.

Neoadjuvant chemoradiation (CRT) has been established as the standard treatment for resectable esophageal cancer, improving overall survival compared to surgery alone [1]. Additionally, neoadjuvant CRT can result in a pathologic complete response (pCR) in approximately one-third of patients [1], a highly favorable prognostic factor associated with improved survival and disease-free survival [2,3].

While CRT plays an integral part in the management of esophageal cancers, it is not without risk of treatment-associated toxicities, including effects on host immunity. Cells of lymphoid origin, in particular, are extremely sensitive to ionizing radiation exposure, and radiotherapy has been shown to suppress the immune system independent of other systemic therapies, even at low doses when given in a fractionated manner [4,5].

Lymphocytopenia is associated with worse outcomes in patients with multiple cancer types. Recent studies have demonstrated a critical role of lymphocytes in promoting systemic immune response against tumors. The presence of tumor infiltrating lymphocytes predicts response to neoadjuvant treatment and is associated with favorable cancer outcomes [6,7]. Several studies in rectal cancer have suggested that lymphopenia during CRT is associated with poor pathologic response in rectal cancer [8–11]. However, whether circulating lymphocyte levels is predictive of pathologic response to neoadjuvant CRT in esophageal cancer patients is unknown.

* Corresponding authors at: Department of Radiation Oncology, Arizona Health Sciences Center, 1501 N. Campbell Avenue, PO Box 245081, Tucson, AZ 85724, United States (C.C. Hsu). Department of Radiation Oncology, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Blvd, Houston, TX 77030, United States (S.H. Lin).

E-mail addresses: cchsu@email.arizona.edu (C.C. Hsu), shlin@mdanderson.org (S.H. Lin).

https://doi.org/10.1016/j.radonc.2018.02.025
0167-8140/

In this study, we examined the relationship between ALC nadir during neoadjuvant CRT and pathologic response to treatment in esophageal cancer.

Methods and materials

Patient selection

Patients for this study were selected from a cohort of patients who were treated with neoadjuvant CRT followed by surgery for esophageal cancer at a single tertiary cancer center from 2007 to 2013. Patients were included if they had pathologic confirmation of Stage I–IVA esophageal cancer, completed CRT to 50.4 Gy, and had at least 3 documented weekly ALC values during CRT. Complete pathologic response (pCR) was defined as no viable tumor cells at surgical resection. All surgical specimens were centrally reviewed.

Statistical methods

ALC values (cells $\times 10^3/\mu l$) were obtained prior to, during (weekly), and one month after CRT. To visualize the peripheral blood immune cell trends during CRT, cell counts were plotted with respect to time during CRT in weeks. The minimum cell count during CRT was identified as the nadir. ALC nadir for all patients were divided into tertiles and assessed for corresponding pCR rate. An ALC nadir threshold of $0.35 \times 10^3/\mu L$ corresponding to the top tertile differentiated between groups of significantly different pCR rates (Fig. 1). We therefore defined ALC nadir $>0.35 \times 10^3/\mu L$ as "high" and $<0.35 \times 10^3/\mu L$ as "low" ALC nadir. Comparison of continuous and categorical variables by pCR was assessed by ANOVA and Pearson's chi-square, respectively. Univariate and multivariate logistic regression was used to model possible predictors of pCR including ALC (high vs. low), gender, disease stage, histology, tumor >5 cm, radiation dose >50 Gy, radiation modality, induction chemotherapy, and chemotherapy type. Multivariate logistic regression was performed to provide model for predictors of a high ALC nadir $>0.35 \times 10^3/\mu L$. Dose–volume histogram parameters and mean body dose (MBD) were extracted and compared between patients with IMRT vs. PBT, and multivariate models with and without adjustment for MBD were compared. All statistical tests are two-sided, and analyses were performed using the STATA software package (version 14; StataCorp, College Station, TX).

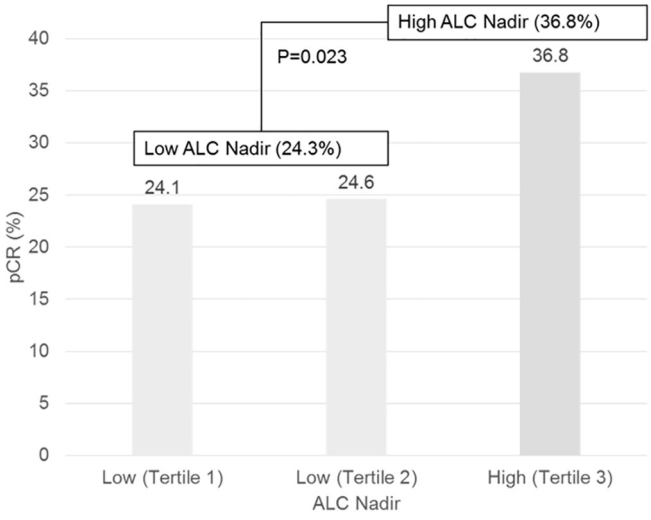

Fig. 1. Pathologic complete response rates by ALC nadir tertile. pCR was significantly higher in patients in the highest tertile compared to those in the lower tertiles.

Results

Patient characteristics

Baseline characteristics of the patients are listed in Table 1. A total of 328 patients were treated with trimodality therapy from 2007 to 2013; 15 patients were excluded who had incomplete blood work. Therefore, a total of 313 patients were included in the analysis cohort. The mean age at diagnosis was 59 years. The majority of the tumors was located in the lower esophagus (97.7%) and was adenocarcinomas (95%). Thirty nine percent were Stage I–II, 59% Stage III, and 4% Stage IVA with a mean tumor length of 5.4 cm. The majority (67%) of patients underwent Intensity-Modulated Radiation Therapy (IMRT), and 40% had induction chemotherapy prior to CRT. The most commonly used concurrent chemotherapy regimen was a taxane and 5-Fluorouracil (5-FU) doublet (43%) followed by platinum and 5-FU combination (39%). All patients subsequently underwent surgical resection after completing CRT, with median time from completion of CRT to surgery of 56.5 days (interquartile range: 46.5–74 days).

Lymphocyte counts during CRT

During CRT, lymphocyte count declined each week of treatment and generally reached a plateau by the end of treatment (Fig. 2).

Table 1
Baseline patient, tumor, and treatment characteristics.

Characteristic	No. of Pts (n = 313)
Mean age at diagnosis, yrs (SD)	59.3 (10.8)
Gender	
Male	278 (88.8%)
Female	35 (11.2%)
Comorbidities	
CAD, *n* (%)	37 (12%)
DM, *n* (%)	44 (14%)
Current smoker, *n* (%)	66 (21%)
Tumor length (cm), mean (SD)	5.4 (2.4)
Tumor location	
Upper/mid	8 (2.3%)
Lower	305 (97.7%)
Overall stage	
Stage I	4 (3%)
Stage IIA	103 (33%)
Stage IIB	10 (3%)
Stage III	184 (59%)
Stage IVA	12 (4%)
Tumor histology	
Squamous	15 (5%)
Adenocarcinoma	298 (95%)
Tumor differentiation	
Well-moderate	147 (47%)
Poor	166 (53%)
Radiation modality	
IMRT	209 (67%)
Proton	104 (33%)
Radiation dose (Gy), mean (SD)	50 (1.9)
induction chemo	124 (40%)
Concurrent chemo regimen	
1. Taxane/5-FU	135 (43%)
2. Platinum/taxane	34 (11%)
3. Platinum/5-FU	121 (39%)
4. Other	23 (7%)

Abbreviations: CAD = coronary artery disease, DM = diabetes mellitus, IMRT = intensity modulated radiation therapy.

Please cite this article in press as: Fang P et al. High lymphocyte count during neoadjuvant chemoradiotherapy is associated with improved pathologic complete response in esophageal cancer. Radiother Oncol (2018), https://doi.org/10.1016/j.radonc.2018.02.025