BRIEF REPORT

Impact of Lymphopenia Recovery After Chemoradiotherapy on Durvalumab Consolidation Therapy in Stage III NSCLC

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ABSTRACT

Introduction: Durvalumab maintenance therapy after definitive concurrent chemoradiotherapy (CRT) is the standard treatment modality for stage III NSCLC. Although severe treatment-related lymphopenia (TRL) during CRT may impair the efficacy of subsequent durvalumab therapy, data on the effect of TRL recovery on consolidation durvalumab therapy are lacking.

Methods: This retrospective study evaluated patients with unresectable stage III NSCLC treated with durvalumab after concurrent CRT. The patients were enrolled across nine institutes throughout Japan between August 2018 and March 2020. The effect of TRL recovery on survival was evaluated. The patients were divided into two groups on the basis of their lymphocyte recovery status: the recovery group involved patients who did not experience severe TRL or experienced TRL but exhibited lymphocyte count recovery at durvalumab initiation, and the nonrecovery group involved patients who experienced severe TRL and did not exhibit lymphocyte count recovery on durvalumab initiation.

Results: Among the 151 patients evaluated, 41 (27%) and 110 (73%) patients were classified into the recovery and the nonrecovery groups, respectively. The nonrecovery group had significantly worse progression-free survival than the recovery group (21.9 mo versus not reached, $p = 0.018$). Recovery from TRL ($p = 0.027$) and high pre-CRT lymphocyte count ($p = 0.028$) independently influenced progression-free survival.

Conclusions: Baseline lymphocyte count and recovery from TRL at the start of durvalumab therapy were predictive factors for survival outcomes in patients with NSCLC treated with durvalumab consolidation after concurrent CRT.

Keywords: Chemoradiation; Durvalumab; Lymphocyte Count; Stage III; Treatment-related lymphopenia

Introduction

Treatment-related lymphopenia (TRL) is associated with poor survival outcomes among patients with lung cancer treated with radiotherapy.[1] In the era of immunotherapy, durvalumab maintenance therapy after definitive concurrent chemoradiotherapy (CRT) has become the standard treatment modality for stage III NSCLC.[2] Several studies have recently indicated that severe TRL during CRT may impair the efficacy of subsequent durvalumab maintenance therapy in this population.[3,4] However, data on the association between recovery from severe TRL and the efficacy of durvalumab treatment are currently lacking. Thus, the present study aimed to investigate the impact of the recovery status from TRL on the efficacy of subsequent durvalumab treatment in patients with stage III NSCLC. Given that lymphocytes are the key effectors of cancer immunotherapy, we hypothesized that recovery from TRL at the start of durvalumab treatment may improve the efficacy of subsequent durvalumab consolidation.

Materials and Methods

This multicenter retrospective study was approved by the appropriate ethics review boards of each participating institution. This retrospective study evaluated patients with unresectable stage III NSCLC treated with at least one dose of durvalumab after concurrent CRT. The patients were enrolled across nine institutes throughout Japan between August 2018 and March 2020. Patients with a history of autoimmune disease, oncogenic driver mutations, or poor Eastern Cooperative Oncology Group performance status (PS) ($\geq$2) were excluded. Clinicodemographic patient characteristics, including PS, smoking status, histology, programmed cell death ligand-1 expression, radiotherapy dose, and lymphocyte count, were collected from the medical records. Lymphocyte counts were collected at three-time points: before CRT, at the nadir during CRT, and at the time of durvalumab initiation. The patients were divided into two groups on the basis of their lymphocyte recovery status: the recovery group involved patients who did not experience severe TRL or experienced TRL but exhibited lymphocyte count recovery at durvalumab initiation, whereas the nonrecovery group involved patients who experienced severe TRL and did not exhibit lymphocyte count recovery on durvalumab initiation. Severe TRL during CRT and lymphocyte count recovery at the start of durvalumab were defined as lymphocyte counts of less than 500/μL and greater than or equal to 1500/μL, respectively.

Progression-free survival (PFS) and overall survival (OS) were both measured from the start of durvalumab therapy. PFS and OS were estimated by generating Kaplan-Meier survival curves and were compared between the two groups using the log-rank test. Wilcoxon rank-sum test, Pearson's chi-square test, and Fisher's exact test were used to compare clinical features between the two groups. Univariate and multivariate analyses were performed using the Cox proportional hazard model. Variables with p value less than 0.1 on univariate analysis were included in the multivariate Cox model analysis, with known risk factors for the outcome and severe lymphopenia as a dichotomous variable. All statistical analyses were conducted using the R software version

Table 1. Patient and Treatment Characteristics

Characteristics	Overall (N = 151)	Recovery Group (n = 41)	Nonrecovery Group (n = 110)	*p* Value
Age (IQR), y	69 (62-74)	67 (62-71)	70 (62-75)	0.12
Sex, n (%)				0.23
F	34 (23)	6 (15)	28 (25)	
M	117 (77)	35 (85)	82 (75)	
Performance status, n (%)				0.55
0	55 (36)	17 (41)	38 (35)	
1	96 (64)	24 (59)	72 (65)	
Smoking status, n (%)				0.67
Current/former	144 (95)	40 (98)	104 (95)	
Never	7 (5)	1 (2)	6 (5)	
Histology, n (%)				0.87
Squamous	72 (48)	20 (49)	52 (47)	
Nonsquamous	79 (52)	21 (51)	58 (53)	
Stage, n (%)				0.65
IIIA	82 (54)	24 (59)	58 (53)	
IIIB / IIIC	69 (46)	17 (41)	52 (47)	
PD-L1 status,[a] n (%)				0.10
≥ 50%	59 (45)	16 (48)	43 (43)	
1%-49%	46 (35)	7 (21)	39 (39)	
< 1%	27 (20)	10 (30)	17 (17)	
RT dose, Gy, n (%)				0.62
<60	2 (1.3)	1 (2)	1 (1)	
60-66	148 (98)	40 (98)	108 (98)	
>66	1 (0.7)	0 (0)	1 (1)	
Time from RT to durvalumab, n (%)				0.10
≤14 d	66 (44)	13 (32)	53 (48)	
>14 d	85 (56)	28 (68)	57 (52)	
Baseline ALC (IQR), /uL	1517 (1230-1994)	1910 (1402-2434)	1430 (1112-1880)	<0.001

[a]Data were unavailable in 19 cases.
ALC, absolute lymphocyte count; F, female; IQR, interquartile range; M, male; PD-L1, programmed death ligand 1; RT, radiotherapy.

4.2.1 (R Core Team, Vienna, Austria). All *p* values were on the basis of a two-sided hypothesis, and a *p* value of less than 0.05 was considered statistically significant.

Results

In total, 151 patients who received definitive CRT followed by durvalumab maintenance therapy were included. The baseline demographic and clinicopathological characteristics of the patients according to the TRL recovery status are summarized in Table 1. The median age of the overall cohort was 69 years (interquartile range [IQR]: 62–74 years). Most patients were men (77%), had an Eastern Cooperative Oncology Group PS of 1 (64%), and were current or former smokers (95%). Paclitaxel and vinorelbine were the typically used nonplatinum chemotherapy regimens during concurrent CRT, with frequencies of 45% and 28%, respectively. The median radiotherapy dose was 60 Gy (IQR: 60–66 Gy). The median number of durvalumab administrations was 19 (IQR: 7–24). Overall, 41 patients (27%) were classified into the recovery group and 110 patients (73%) were classified into the nonrecovery group. The baseline lymphocyte counts before CRT was significantly lower in the nonrecovery group than in the recovery group (1430/μL versus 1910/μL, $p < 0.001$), but there were no differences in other characteristics between the groups (Table 1). Figure 1 shows the dynamic changes in lymphocyte counts at three-time points according to the duration of treatment efficacy. The results indicated that patients with a shorter duration of efficacy had inadequate recovery from the lymphocyte nadir on the initiation of durvalumab therapy.

The median follow-up period was 27.2 months (Kaplan-Meier estimate). The median PFS was 27.3 months (95% confidence interval [CI]: 21.4– not reached); the median OS was not reached; and the 2-year OS rate was 71.7% (95% CI: 64.6%–79.7%). The nonrecovery group had significantly worse PFS than the recovery group (21.9 versus not reached; $p = 0.018$) (Fig. 2*A*). In addition, among patients with lymphocyte counts of at least 1500/μL at baseline before CRT, the nonrecovery group had significantly worse PFS than the recovery group (13.3 versus not reached, $p = 0.0013$) (Fig. 2*B*). Multivariate analysis of tumor proportion score (<1% versus ≥1%), histology (squamous versus

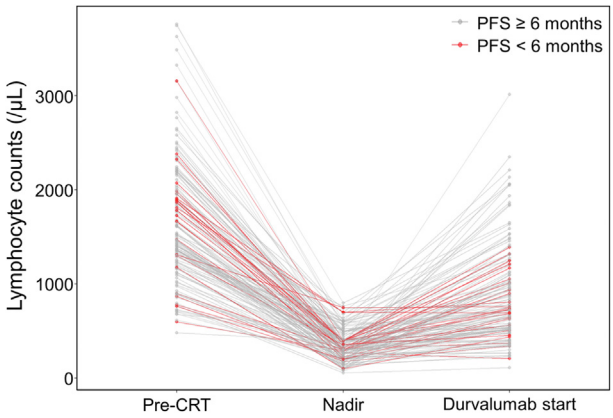

Figure 1. Dynamic changes in lymphocyte count at the three-time points according to the duration of durvalumab treatment efficacy. CRT, chemoradiotherapy; PFS, progression-free survival.

nonsquamous), pre-CRT lymphocyte counts ($<1500/\mu$L versus $\geq 1500/\mu$L), the interval between the end of radiotherapy to durvalumab initiation (≤ 14 d versus >14 d), and recovery status from TRL (recovery versus non-recovery) exhibited that recovery status from TRL (hazard ratio = 2.10, 95% CI: 1.08–4.07, $p = 0.027$) and pre-CRT lymphocyte counts (hazard ratio = 1.76, 95% CI: 1.06–2.90, $p = 0.028$) were independently associated with PFS.

Discussion

This study investigated the effects of TRL recovery after CRT on the efficacy of subsequent durvalumab therapy in clinical practice. This study found that the recovery group had significantly better PFS than the nonrecovery group. The results were found to be consistent when excluding patients with low pre-CRT lymphocyte counts of less than $1500/\mu$L (who were less likely to be classified as part of the recovery group). Moreover, multivariate analysis revealed recovery of TRL and high pre-CRT lymphocyte count to be independent factors associated with better PFS. Our results suggest that both the baseline lymphocyte count and recovery from the lymphocyte nadir on initiation of durvalumab therapy were useful predictive markers of treatment outcomes of durvalumab.

Various factors predict the clinical efficacy of immune checkpoint inhibitors; these include body composition, peripheral lymphocyte count, neutrophil-to-lymphocyte ratio, and advanced lung cancer inflammation index.[5–9] In patients with stage III NSCLC, a limited number of studies have investigated the relationship between lymphocyte count and the efficacy of consolidation durvalumab.[3,4,10,11] Several studies indicated that severe TRL may impair the efficacy of subsequent durvalumab maintenance therapy in this population.[3,4] In these studies, the baseline pre-CRT lymphocyte count was identified as a predictor for the development of severe TRL. Meanwhile, a retrospective study of 113 patients reported that no CRT-induced changes but baseline pre-CRT lymphocyte count was associated with PFS in patients treated with CRT and consolidative durvalumab.[11] However, these previous data consistently suggest that baseline lymphocyte counts before CRT are a key factor that could influence the outcomes of subsequent durvalumab treatment. Furthermore, another retrospective study of 66 patients reported the relationship between survival and persistent lymphopenia in patients with stage III NSCLC receiving maintenance immunotherapy (durvalumab accounting for 94%)[10]; in this study by Cho et al.,[10] persistent lymphopenia, defined as less than $500/\mu$L at 3 months after CRT, was related to poor survival outcomes. In addition, recovery from lymphopenia was significantly associated with pretreatment lymphocyte count ($p = 0.03$). Our study differs from these previous studies in that it evaluated the relationship between recovery status from lymphopenia at the start of durvalumab treatment and the efficacy of

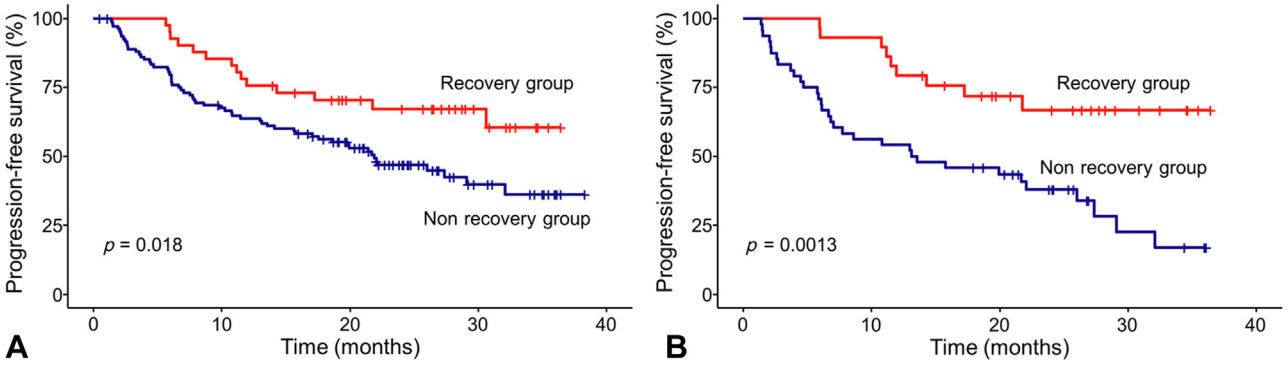

Figure 2. Kaplan-Meier curves of progression-free survival by recovery status from treatment-related lymphopenia. (*A*) All patients (N = 151). (*B*) Patients with lymphocyte counts of greater than or equal to $1500/\mu$L at baseline before chemoradiotherapy (n = 77).

durvalumab treatment, with a larger sample size and longer follow-up period.

CRT-induced immunogenic cell death leads to the activation of cytotoxic T cells, and radiotherapy has been positioned as a synergistic partner in cancer immunotherapy rather than as a mere local treatment.[12] However, it can have a detrimental effect on the immune system, particularly on circulating blood lymphocyte levels. Furthermore, considering that chemotherapy exerts both immunogenic and immunosuppressive effects, the dose and schedule of chemotherapeutic drugs may influence the antitumor immune responses.[13] Factors known to contribute to lymphopenia after CRT, such as chemotherapy delivery, radiation dose, radiation field, planning target volume, and a number of fractions, may also be important from an immunologic perspective.[14,15] Therefore, tailoring CRT regimens, such as the optimal timing, radiation dose, fractionation, target volume, and chemotherapy dose and schedule, to spare the immune system and optimize subsequent durvalumab therapy may be essential for improving patient outcomes.[13,16] Furthermore, one report notably indicated that in patients with locally advanced NSCLC, severe TRL at the start of consolidation immunotherapy was associated with rapid disease progression.[3] Although TRL is known to negatively impact survival in patients with NSCLC treated with radiation,[1] clinicians should keep in mind that TRL after CRT may be a critical factor for the treatment efficacy, particularly in patients who are scheduled to receive durvalumab consolidation therapy.

This study had several limitations. First, its retrospective design is associated with a risk of bias, which precludes definite conclusions. Second, only the total dose of radiotherapy was determined, and other information on radiation (e.g., irradiation technique) was not evaluated. Third, although laboratory data obtained within two weeks of treatment start were collected, the frequency of lymphocyte count measurement during CRT was at the discretion of physicians and was not standardized across institutions. Finally, lymphocyte counts were measured at only three points in this study, and the subsequent trend after durvalumab initiation was not followed. The possibility of some patients having a decrease in lymphocyte counts again after durvalumab initiation, which could affect the interpretation of the study results, could not be ruled out. Therefore, our study should be regarded as a hypothesis for future studies.

In conclusion, we found that baseline lymphocyte count and recovery from TRL at the start of durvalumab therapy were associated with survival outcomes in NSCLC patients treated with durvalumab consolidation after concurrent CRT. Further studies are warranted to validate our findings.

Credit Authorship Contribution Statement

Tomoki Kuge, Takayuki Shiroyama, Izumi Nagatomo: Conceptualization, Methodology, Data curation, Formal analysis, Investigation, Methodology, Resources, Writing—original draft, Writing—review and editing.

Akihiro Tamiya, Motohiro Tamiya, Masaki Kanazu, Yuhei Kinehara, Tsunehiro Tanaka, Osamu Morimura, Toshie Niki, Satoshi Tetsumoto, Kazuhiko Hayashi: Data curation, Investigation, Resources, Writing—review & editing.

Kazumi Nishino, Atsushi Kumanogoh: Writing—review & editing.

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