

The absolute lymphocyte/monocyte ratio recovery during ABVD treatment cycles is not significantly impacted by the use of myeloid growth factors and predicts clinical outcomes in classical Hodgkin lymphoma regardless of their use

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Abstract: Risk stratification of patients with classical Hodgkin lymphoma (cHL) remains sub-optimal. The ratio of the absolute lymphocyte count (ALC) to absolute monocyte count (AMC) both at diagnosis and during subsequent recovery from serial cycles of chemotherapy predicts survival in cHL, and possesses advantages over other commonly used prognostic markers. Myeloid growth factors (MGFs), while not strongly recommended for use in adriamycin, bleomycin, vinblastine, and dacarbazine (ABVD) treatment cycles, are not uncommonly used to prevent the negative consequences of neutropenia. The effect that MGFs have on the ALC/AMC ratio during ABVD treatment cycles, if any, remains unclear. We retrospectively evaluated 208 patients with cHL, who were diagnosed, treated, and followed at Mayo Clinic Rochester between 1990 and 2014, and who had quantifiable records for the use of MGFs during ABVD treatment cycles. Having an ALC/AMC ratio <1.1 during all treatment cycles was confirmed as being a negative predictor of overall and progression free survival (hazard ratio [HR] 0.06, 95% confidence interval [CI] 0.03–0.14 and HR 0.08, 95% CI 0.04–0.17, respectively). Data on both the ALC/AMC ratio and use of MGFs were available for 1,979 half treatment cycles. When stratified to whether or not MGFs were given, the change in the ALC/AMC ratio as compared to the prior half cycle was found to be statistically insignificant ($P=0.3445$). No survival advantage was found with the administration of MGFs in any cycle of therapy (log rank $P=0.5713$). Our data validate the prognostic significance of having an ALC/AMC ratio of ≥ 1.1 regardless of the use of MGFs.

Keywords: myeloid growth factors, classical Hodgkin lymphoma, survival ALC/AMC ratio, ABVD chemotherapy

Introduction

While the majority of patients with classical Hodgkin lymphoma (cHL) obtain favorable metrics of survival in comparison to other hematologic malignancies, the risk stratification of these patients remains suboptimal.¹ Identification of patients at reduced risk of treatment failure remains particularly important in order to consider treatment reduction in chemotherapy cycles and adjuvant radiation dose. Reduction in therapy in such patients would not lead to worse cHL outcomes and could lead to long-term risk reduction for secondary malignancies and other complications of survivorship.²

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In the age of cost-conscious medicine, markers of disease risk stratification that are relatively low-cost and easy to obtain are increasingly desirable. It has previously been shown that the peripheral blood absolute lymphocyte count (ALC) to absolute monocyte count (AMC) ratio ($R^{ALC/AMC}$) at diagnosis can predict outcomes in cHL.^{3,4} Along with the observation that tumor associated macrophages influence clinical outcomes, the $R^{ALC/AMC}$ highlights the importance of the relationship between the host immune system and innate tumor biology in the natural course of cHL.⁵ The limitation of the above markers, as well as the International Prognostic Score at diagnosis and stratification by interim positron emission tomography scan, lies in their inability to continuously assess host/tumor immune interaction during treatment cycles, as they are obtained at a single time point in the course of therapy.^{6,7} We have previously shown that the peripheral blood $R^{ALC/AMC}$ during each cycle of therapy in cHL with adriamycin, bleomycin, vinblastine, and dacarbazine (ABVD) possesses prognostic value in predicting clinical outcomes.⁸ The current study aims to validate the use of this easily obtained and inexpensive predictive marker with the concomitant utilization, or lack thereof, of myeloid growth factors (MGFs) (such as filgrastim and pegfilgrastim) during cycles of ABVD in cHL.

MGFs are used in cancer chemotherapy in an attempt to ameliorate the negative consequences of prolonged neutropenia and allow therapy to proceed without dose reduction or delay. Despite a primary increase in neutrophils following their administration, there is also evidence that MGFs affect the bone marrow's output of lymphocytes and monocytes in an uneven ratio, raising concerns that their use could impact the $R^{ALC/AMC}$.⁹ In cHL, ABVD is typically administered in two phases ("a" and "b") on day 1 and day 15 of each cycle, and is considered to have an intermediate risk (10%–20%) of causing febrile neutropenia.¹⁰ Current guidelines consider this intermediate risk an indication for clinicians to consider the use of MGFs, but do not give a strong endorsement for or against their use.¹¹ There is conflicting data regarding both the necessity of MGFs to prevent complications of neutropenia in ABVD, as well as a potential role in increasing the risk of developing bleomycin related pulmonary toxicity.^{12–16} Despite these controversies, the use of MGFs in a real world clinical setting in the treatment of cHL is not uncommon. Validating the prognostic value of the $R^{ALC/AMC}$ during count recovery of repetitive ABVD cycles in the treatment of cHL with or without the use of MGFs, remains an important unanswered question.

Materials and methods

Patients

Two hundred and thirty-two patients with newly diagnosed cHL, treated with ABVD with or without radiation, and followed at Mayo Clinic (Rochester, MN, USA) between the years 1990 and 2014 were retrospectively identified. Patients were not included if they had a pathological diagnosis of nodular lymphocyte-predominant HL, were treated only with radiation or palliative care, had a concomitant autoimmune disease and were receiving immunosuppressive therapy, participated in clinical trials, or if they had HIV. All demographic and clinical information including age, sex, and hematologic labs were obtained from medical records. Institutional Review Board (IRB) approval was obtained in accordance with the Declaration of Helsinki. The $R^{ALC/AMC}$ was obtained from the complete blood cell count (CBC) as previously described.⁸ Information regarding the use or lack of use of MGFs during each ABVD half-cycle, as well as the specific type and dose of growth factor given, was obtained from the computerized chemotherapy records (for ABVD cycles given after 2003) or from a prior paper record system (cycles given prior to 2003).

End point

The primary end point of the study was to assess if MGFs affect the $R^{ALC/AMC}$ recovery during ABVD chemotherapy. The secondary end point was to evaluate if MGFs have any impact on overall survival (OS) and progression-free survival (PFS) in cHL patients treated with ABVD chemotherapy.

The cut-off of an $R^{ALC/AMC} \geq 1.1$ used in this study was based on our previous publications and obtained from the CBC count from a similar automated technology with devices that have included the Coulter STKR, Coulter STKS, Coulter GENS, Coulter LH500, Coulter LH750, Coulter HmX, Coulter AcT Diff5 (Beckman Coulter, Inc., Brea, CA, USA), Sysmex XE5000, Sysmex XE2100, Sysmex 1800, and Sysmex 200 (Sysmex Inc., Kobe, Japan), at each cycle phase of ABVD treatment.^{3,17} The $R^{ALC/AMC}$ was obtained by dividing the absolute lymphocyte count (ALC) over the absolute monocyte count (AMC) from the CBC count at each cycle phase of ABVD chemotherapy.

Prognostic factors

The prognostic factors evaluated in the study included the International Prognostic Score (IPS) at diagnosis for advanced stage patients: age >45 years, albumin <4 g/dL, ALC <600 cells/ μ L or <8% of white blood cell count, hemoglobin <10.5 g/dL, male sex, stage IV and white blood cell count $\geq 15,000$ cells/ μ L; limited versus advanced stage;

treatment modality (combination chemotherapy plus radiation versus chemotherapy alone), use of MGFs during treatment cycles, and the $R^{ALC/AMC}$ during treatment cycles.¹⁸

Statistical analysis

Patient characteristics were described in percentages for nominal variables, while continuous variables were described with median and range. To determine whether the use of MGFs impacted subsequent $R^{ALC/AMC}$ we calculated a $\Delta R^{ALC/AMC}$ value, defined as the change in the ALC/AMC ratio from half ABVD cycle n and half cycle $n-1$. The $\Delta R^{ALC/AMC}$ value was then stratified into whether or not the patient received a MGF between the date of the CBC count determining the $R^{ALC/AMC}$ for cycle $n-1$ and cycle n which was typically obtained when the patient came in for the following half cycle. Specifically, for cycle 1a the $\Delta R^{ALC/AMC}$ was calculated as the $ALC/AMC^{\text{obtained cycle 1 day15}} - ALC/AMC^{\text{obtained cycle 1 day1}}$. For the last half cycle the $R^{ALC/AMC}$ was taken from a subsequent CBC between 2 and 4 weeks following the last dose of chemotherapy. If no such lab value was available, the last half cycle was not included in the analysis as no $\Delta R^{ALC/AMC}$ could be accurately calculated. The Wilcoxon rank sum test was used to compare the mean " $\Delta R^{ALC/AMC}$ " for all patients and all cycles depending on whether or not MGFs were given for the particular half cycle in which each individual $\Delta R^{ALC/AMC}$ was calculated. For each individual half cycle of ABVD a Wilcoxon rank sum test was performed to compare the mean $\Delta R^{ALC/AMC}$ for that cycle depending on whether or not MGFs were given. Also, for each individual half cycle of ABVD the Wilcoxon rank sum test was performed on groups of patients with a $R^{ALC/AMC} \geq 1.1$ as well as <1.1 for cohorts of patients who did and did not receive MGFs for that half cycle. Survival curves were constructed using Kaplan–Meier estimates and the log-rank test was used to detect differences. Cox proportional hazard analysis was performed for both univariate and multivariate factors, including the use and number of cycles MGFs were given, to assess their predictability on PFS and OS. JMP version10 (SAS Institute Inc, Cary, NC, USA) was used for statistical analysis.

Results

Two hundred and eight of the 232 eligible patients were evaluable for inclusion in final analysis. Twenty-four patients were excluded for lack of data on the use of MGFs. In total, 1,979 half treatment cycles were evaluable and had data on the use of MGFs as well as a $R^{ALC/AMC}$ for that cycle phase and the cycle preceding it. Median age at diagnosis was 36 years, and 54% of patients were male. Median follow up for the

entire cohort from diagnosis was 64.5 months (1–270), and was 72 months (10–270) for the 179 patients alive at last follow-up. Overall, 69% of patients received MGFs in any cycle and the median number of half cycles was 3 (0–12). Of the patients who received any MGF, the median number of half cycles in which growth factors were given was 6 (1–12). Twenty-eight percent of patients had greater than or equal to three IPS risk factors at diagnosis, and 54% were treated with chemotherapy alone. The baseline characteristics are detailed in Table 1.

To test whether there was a difference in the $R^{ALC/AMC}$ depending on the use of MGFs, the Wilcoxon rank sum test was performed for each 12 half cycles of ABVD. These results are summarized in Table 2. In all 12 half cycles, there was no statistically significant difference in the $\Delta R^{ALC/AMC}$. When all half cycles were split on the basis of the use of MGFs, an average $\Delta R^{ALC/AMC}$ was calculated for each patient, the Wilcoxon signed rank test showed a P -value of 0.3445 indicating no statistical difference between the two groups.

To confirm our previous reported finding that patients with a $R^{ALC/AMC}$ less than 1.1 in all cycles of therapy have a worse prognosis, survival curves were constructed and shown in Figure 1A. There was no difference in OS between patients who received MGFs and those who did not receive them in any cycle (log rank $P=0.5713$). However, patients who received MGFs in >3 half cycles had statistically superior OS as compared to patients who received MGFs in <3 half cycles (log rank $P=0.0288$) Figure 1B and C. Similar findings were found looking at PFS and are shown in Figure 1D–F respectively.

Cox-proportional hazard analysis focusing on the potential effects of MGFs on OS and PFS showed that the use of MGFs in the majority of individual treatment cycles, as well as the use, or lack of use of MGFs, in any treatment cycle did not impact OS or PFS (Table 3). Multivariate analysis showed that while having a $R^{ALC/AMC} \geq 1.1$ in any cycle as well as having an IPS score <3 at diagnosis strongly predicted survival, the use of MGF in any cycle did not have a statistical impact on OS or PFS (HR [95% CI] 0.80 [0.37–1.79] and 0.74 [0.40–1.40] for OS and PFS, respectively).

Discussion

The $R^{ALC/AMC}$ recovery during ABVD treatment cycles for cHL predicts clinical outcomes. Our current data validate this prognostic biomarker in the setting of MGF use. As there has been preclinical data which has shown a differential increase in lymphocytes and monocytes following MGF administration, it was reasonable to query whether their use has an

Table 1 Baseline patient characteristics (n=208)

Variable	Percentage	Median (range)
Age at diagnosis	–	36 (18–89)
Male sex	54	–
Clinical follow-up (months)	–	64.5 (1–270)
Stage		
I	5.3	–
II	45.2	–
III	28.4	–
IV	21.2	–
Initial treatment		
CT + RT	45.7	–
CT	54.3	–
IPS		
Age (years) ≥ 45	36.0	–
Albumin (g/dL) $n=176 < 4$	47.2	–
Hgb (g/dL) < 10.5	14.9	–
WBC $\times 10^9/L \geq 15$	12.5	–
Male	54	–
Stage IV	21.2	–
IPS factors index ≥ 3	28.4	–
Number of cycles given		
2	8.7	–
3	2.9	–
4	28.8	–
5	2.4	–
6	56.7	–
Received any MGFs	69.7	–
Number of half cycles MGFs given	–	3 (0–12)
Cycle 1A (n=208)		
ALC/AMC ratio	–	2.1 (0.15–85.5)
MGF used	9.0	–
Cycle 1B (n=206)		
ALC/AMC ratio	–	2.26 (0.22–37.5)
MGF used	44.7	–
Cycle 2A (n=204)		
ALC/AMC ratio	–	1.98 (0.22–60.2)
MGF used	40.7	–
Cycle 2B (n=204)		
ALC/AMC ratio	–	1.90 (0.17–26.5)
MGF used	44.6	–
Cycle 3A (n=188)		
ALC/AMC ratio	–	1.88 (0.15–20.8)
MGF used	42.6	–
Cycle 3B (n=188)		
ALC/AMC ratio	–	1.67 (0.15–9.83)
MGF used	47.8	–
Cycle 4A (n=183)		
ALC/AMC ratio	–	1.67 (0.20–19.4)
MGF used	43.1	–
Cycle 4B (n=181)		
ALC/AMC ratio	–	1.80 (0.26–5.79)
MGF used	40.2	–
Cycle 5A (n=122)		
ALC/AMC ratio	–	1.78 (0.32–9.25)
MGF used	52.5	–
Cycle 5B (n=121)		
ALC/AMC ratio	–	1.70 (0.33–14.22)
MGF used	50.4	–

(Continued)

Table 1 (Continued)

Variable	Percentage	Median (range)
Cycle 6A (n=118)		
ALC/AMC ratio	–	1.63 (0.30–30.00)
MGF used	48.3	–
Cycle 6B (n=116)		
ALC/AMC ratio	–	1.63 (0.39–10.00)
MGF used	41.4	–

Abbreviations: Hgb, hemoglobin; CT, chemotherapy; RT, radiation therapy; IPS, International Prognostic Score; MGF, myeloid growth factor; ALC, absolute lymphocyte count; AMC, absolute monocyte count; WBC, white blood cell count.

identifiable impact on the following half cycle's CBC count and $R^{ALC/AMC}$, as this could have a confounding effect on the cutoff previously reported.⁹ However, our data show that in the majority of cycles there is no statistical difference in the $R^{ALC/AMC}$ as compared to the most recent cycle whether MGFs were used or not. As there are other unmeasurable factors that can influence bone marrow production of non-neutrophilic leukocytes, such as exposure to certain pathogens, we used the Wilcoxon rank sum test to compare groups as the data did not satisfy an assumed normal distribution. The limitation of our study is in its retrospective design and the long period of time (14 years) over which data were collected. Future prospective confirmatory studies should be undertaken to confirm our findings.

Our data show a small statistically significant OS and PFS benefit when patients are dichotomized by whether they received >3 half cycles of ABVD inclusive of MGFs.

Table 2 Comparison of the $\Delta R^{ALC/AMC}$ dependent on MGF status for 12 ABVD half cycles

Cycle (n)	Wilcoxon rank sum $\Delta R^{ALC/AMC}$ (MGF vs no MGF in $\frac{1}{2}$ cycle) P-value	Subgroup P-value	Subgroup P-value
1A (208)	0.1921	$R^{ALC/AMC} \geq 1.1$ 0.2657	$R^{ALC/AMC} < 1.1$ 0.4922
1B (206)	0.3452	0.1658	0.1106
2A (204)	0.4512	0.1221	0.0315*
2B (204)	0.3864	0.4973	0.4524
3A (188)	0.2612	0.8267	0.1746
3B (188)	0.6263	0.6355	0.8135
4A (183)	0.2676	0.3234	0.2652
4B (181)	0.1054	0.2738	0.0852
5A (122)	0.6127	0.8618	0.7985
5B (121)	0.0851	0.1164	0.5338
6A (118)	0.1523	0.3009	0.4277
6B (116)	0.6419	1.0000	0.4440

Note: * indicates statistical significance of P-value < 0.05 of Wilcoxon rank sum test comparing groups indicated in columns.

Abbreviations: ALC, absolute lymphocyte count; AMC, absolute monocyte count; ABVD, adriamycin, bleomycin, vinblastine, and dacarbazine; MGF, myeloid growth factor; vs, versus.

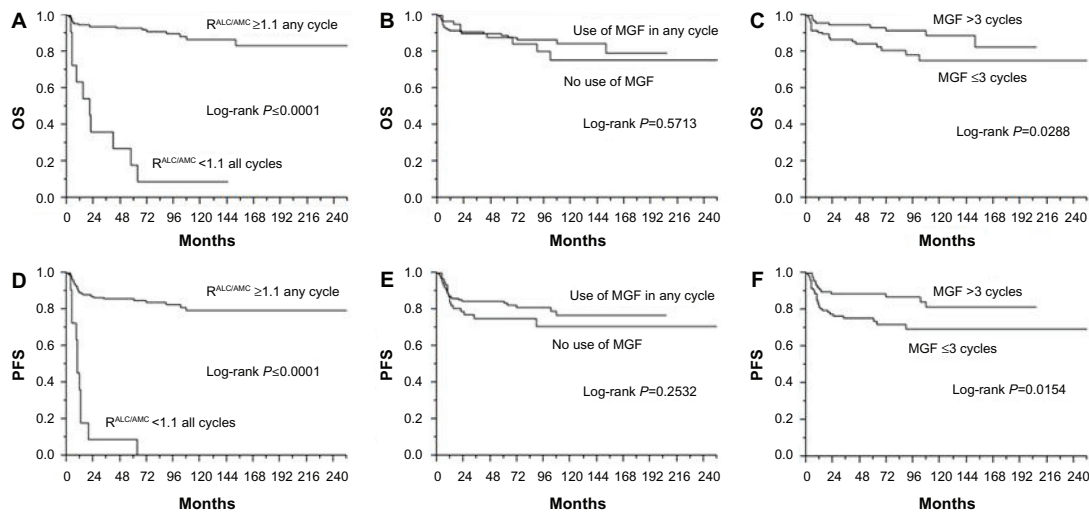


Figure 1 Overall (A-C) and progression free survival (D-F) dependent on $R^{ALC/AMC}$ and MGF use status.

Abbreviations: ALC, absolute lymphocyte count; AMC, absolute monocyte count; MGF, myeloid growth factor; OS, overall survival; PFS, progression free survival.

The clinical significance of this observation is minimal, and it should be noted that patients who received no MGFs had equivalent clinical outcomes to those who received any MGFs. The lack of impact of MGFs on OS is consistent with other reported literature, and clinical guidelines on their use.¹⁹

The observation of the $R^{ALC/AMC}$ as a predictor of OS has been shown to hold true in other disease settings in addition to cHL.²⁰ The specter of being able to manipulate the $R^{ALC/AMC}$ for therapeutic advantage is appealing, if done in a way that meaningfully adjuncts the relationship of the host immune system to the tumor micro-environment. Our data show that

Table 3 Univariate and multivariate analysis for overall and progression free survival

Variable	OS		PFS	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Univariable analysis				
Cycle 1A use of MGFs	2.11 (0.71–5.10)	0.16	2.02 (0.82–4.26)	0.12
Cycle 1B use of MGFs	1.17 (0.56–2.45)	0.67	0.88 (0.47–1.61)	0.68
Cycle 2A use of MGFs	0.97 (0.45–2.06)	0.95	0.93 (0.49–1.72)	0.82
Cycle 2B use of MGFs	0.32 (0.12–0.74)	0.007*	0.30 (0.14–0.61)	0.001*
Cycle 3A use of MGFs	0.45 (0.18–1.04)	0.06	0.46 (0.22–0.90)	0.022*
Cycle 3B use of MGFs	0.37 (0.14–0.86)	0.020*	0.43 (0.21–0.83)	0.012*
Cycle 4A use of MGFs	0.72 (0.90–1.62)	0.43	0.56 (0.27–1.08)	0.09
Cycle 4B use of MGFs	0.46 (0.17–1.14)	0.09	0.59 (0.28–1.18)	0.14
Cycle 5A use of MGFs	0.86 (0.29–2.52)	0.78	0.59 (0.27–1.26)	0.17
Cycle 5B use of MGFs	0.55 (0.17–1.66)	0.29	0.48 (0.20–1.05)	0.07
Cycle 6A use of MGFs	0.47 (0.13–1.50)	0.21	0.46 (0.19–1.04)	0.06
Cycle 6B use of MGFs	0.64 (0.17–2.05)	0.47	0.50 (0.20–1.16)	0.11
Use of MGFs in any cycle	0.80 (0.38–1.80)	0.58	0.70 (0.38–1.33)	0.27
Number of cycles (0–12) MGFs used	0.31 (0.08–1.01)	0.05	0.36 (0.12–0.95)	0.039*
Any cycle $R^{ALC/AMC} \geq 1.1$	0.06 (0.03–0.14)	<0.0001*	0.08 (0.04–0.17)	<0.0001*
IPS ≥ 3 at diagnosis	4.25 (2.04–9.13)	0.0001*	2.86 (1.56–5.22)	0.0008*
Multivariable analysis				
Use of MGF in any cycle	0.80 (0.38–1.82)	0.5829	0.74 (0.40–1.42)	0.36
Any cycle $R^{ALC/AMC} \geq 1.1$	0.10 (0.04–0.24)	<0.0001*	0.11 (0.05–0.25)	<0.0001*
IPS ≥ 3 at diagnosis	2.59 (1.13–5.97)	0.0245*	2.00 (1.03–3.84)	0.041*

Note: * indicates $P < 0.05$.

Abbreviations: OS, overall survival; PFS, progression free survival; HR, hazard ratio; CI, confidence interval; MGF, myeloid growth factor; ALC, absolute lymphocyte count; AMC, absolute monocyte count; IPS, International Prognostic Score.

the use of MGFs during ABVD does not consistently have an altering effect on the $R^{ALC/AMC}$, and does not have a clinically significant influence on OS and PFS. The $R^{ALC/AMC}$ is not meaningfully affected by the use of MGFs during cycles of ABVD in cHL.

Disclosure

The authors declare no conflicts of interest in this work.

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