The lymphocyte to monocyte ratio improves the IPI-risk definition of diffuse large B-cell lymphoma when rituximab is added to chemotherapy

Alessandro Rambaldi,1* Cristina Boschini,1 Giuseppe Gritti,1 Federica Delaini,1 Elena Oldani,1 Andrea Rossi,1 Anna Maria Barbui,1 Daniele Caraccio,2 Marco Ladetto,2 Angela Gueli,3 Alberto De Crescenzo,4 Roberto Passera,2 Liliana Devizzi,5 Caterina Patti,6 Alessandro Massimo Gianni,5 and Corrado Tarella2,3

The peripheral blood lymphocyte to monocyte ratio (LMR) at diagnosis can be clinically relevant in patients with diffuse large B-cell lymphoma (DLBCL). We reviewed the outcome of 1,057 DLBCL patients followed from 1984 to 2012 at four centers. LMR was analyzed as a clinical biomarker by receiver-operating characteristic (ROC) analysis and Harrell’s C-statistics. Patients were characterized by a median age of 61 years, International Prognostic Index (IPI) score of >2 in 39%, and were treated with a rituximab-containing chemotherapy in 66%. LMR proved strongly predictive for survival in patients treated with rituximab-based programs, but not in those receiving chemotherapy alone. Additionally, an LMR value of ≤2.6 (as determined by ROC analysis) was associated with a worst performance status, a higher lactate dehydrogenase (LDH) level, an advanced clinical stage, and a higher IPI score (P = 0.000). In patients treated with rituximab-supplemented chemotherapy programs, an LMR value of ≤2.6 was found in most of the primary refractory patients (75%) which proved as the best cutoff to predict both response and survival (P = 0.018). Finally, multivariate analysis and Harrell’s C-statistics confirmed the IPI-independent role of LMR on survival (P = 0.0000). In conclusion, LMR is a potent predictor of clinical response and survival in DLBCL treated with rituximab-containing chemotherapy. Am. J. Hematol. 88:1062–1067, 2013. © 2013 Wiley Periodicals, Inc.

Introduction

The clinical outcome of diffuse large B-cell lymphoma (DLBCL), the most common subtype of non-Hodgkin’s lymphomas, has significantly improved by the introduction of rituximab [1–4]. However, a significant proportion of patients eventually die of the disease and extensive studies have been conducted over the last 20 years to identify novel biomarkers characterizing patients at poor prognosis. Among these, gene expression profiling (GEP) and mutational analyses have provided crucial information as to the intrinsic heterogeneity of lymphoma cells [5,6] as well as to the role of the tumor microenvironment [7,8]. Unfortunately, in the daily clinical practice, GEP still has limited applicability and immunohistochemistry-based algorithms proposed as its possible surrogates [9] showed limited reproducibility and are not yet currently used as a decision tool [10,11]. Thus, the evaluation of prognosis by simple clinical parameters as originally proposed by the International Prognostic Index (IPI) score [12] still remains the current clinical standard even in the rituximab era [3,13].

The number and type of lymphocytes and monocytes/macrophages detectable in the peripheral blood and in the lymph nodes of patients with Hodgkin’s [14,15] and non-Hodgkin’s [7,16,17] lymphomas have been extensively investigated and immunohistologically-based algorithms proposed as its possible surrogates [9] showed limited reproducibility and are not yet currently used as a decision tool [10,11]. Thus, the evaluation of prognosis by simple clinical parameters as originally proposed by the International Prognostic Index (IPI) score [12] still remains the current clinical standard even in the rituximab era [3,13].

Patients and Methods

Patients

Eligible for this retrospective analysis were patients with a histologically proven diagnosis of DLBCL according to WHO classification with disease at onset, with no previous treatments for lymphoma or other neoplasm in the previous 5 years. Clinical information available prior to treatment included patient age, gender, Eastern Cooperative Oncology Group (ECOG) performance status, physical examinations, systemic B

Additional Supporting Information may be found in the online version of this article.

© 2013 Wiley Periodicals, Inc.
symptoms, complete blood count, biochemical profiles, serum lactate dehydrogenase (LDH) level, Ann Arbor stage, and number of extranodal involved sites determined by bone marrow biopsy, computed tomography (CT) scans of the thorax, abdomen, and pelvic cavity, along with whole-body positron emission tomography (PET)/CT scans for patients referred in the last 5 years. The absolute lymphocyte count (ALC), the absolute monocyte count (AMC), and the absolute LMR were obtained and calculated at diagnosis by a standard automated cell counter. A total number of 1,057 adult patients (≥18 years) treated between February 1984 and March 2012 at four referral Italian hematology centers in Bergamo (n = 702), Torino (n = 182), Milan (n = 88), and Palermo (n = 85) was the object of our analysis.

Study objective, diagnostic parameters, and outcome evaluation

Most patients received standard CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) delivered either at 21- or 14-day interval or CHOP-like regimens weekly [20]. A minority of patients were managed with the high-dose sequential program (HDS), delivered as detailed previously [4,21]. Most of these patients were part of the prospective trials aimed to evaluate the efficacy of the HDS program of primary treatment for high-risk DLBCL [4]. Radiotherapy was delivered following chemotherapy for residual disease or previously bulky disease. Treatment response was defined according to the 1999 International Working Group criteria [22].

Statistical analysis

A ROC analysis, widely employed in diagnostic tests but also used for prognostic evaluation, was performed to determine the cutoff of LMR, as previously described. Because standard methods do not exist for deriving ROC curves for time-to-event data, we used occurrence as compared with nonoccurrence of events within 20 years from DLBCL diagnosis as the outcome for the analysis as previously described [18]. Patient characteristics were compared between the main arms, i.e., patients receiving rituximab-supplemented chemotherapy programs vs. those receiving chemotherapy alone, or IPI 0–2 vs. IPI > 2, or LMR > 2.6 vs. LMR < 2.6, using the Pearson χ² test or the Fisher’s exact test for discrete variables and the nonparametric Kruskal–Wallis test for continuous variables [23]. The ability to classify risk in individual patients was assessed by the C-index, which measures the ability to classify individual patients into risk groups at different prognosis by the probability of concordance between the rank of the model prognosis and the rank of the observed outcomes over pairs of population subjects. Specifically, C-index is the concordance probability for any given pair of Subjects i and j, labeled such as i fails while is still event free, i is assigned a poorer prognosis than j. In the presence of right random censoring, the rank between the underlying failure times of a pair of subjects can be determined if, and only if, the shortest time between the two is not censored (comparable pair). As a consequence, the concordance between the rank of predictions and rank of outcome can be assessed only for comparable pairs, and in practice C-index is estimated by the ratio of concordant number of pairs over the total number of comparable pairs [27]. C-index values range from 0.5 (absence of discrimination) to 1 (perfect discrimination). The long-term outcome was assessed in terms of overall survival (OS), disease-free survival (DFS), and event-free survival (EFS). The OS was defined as the time from the start of treatment to death for any cause. The DFS and EFS were defined according to Cheson criteria [22] and analyzed by the Kaplan–Meier method. Patients were censored at the date of last contact, follow-up was updated in September 2012, and all living patients had been observed at least once in the previous 3 months. Differences in survival between groups were identified by generalized log-rank analysis [28]. Univariate and multivariate analyses for survival were performed on several parameters, including sex, age at diagnosis, Ann Arbor stage, ECOG performance status, LDH level, International Prognostic Index (IPI) score, AMC, ALC, and LMR.

Approval for the retrospective review of these records was obtained from the ethic Committees and the study was conducted in accordance with the Italian laws and the Declaration of Helsinki.

Results

LMR at diagnosis correlates with high-risk clinical presentation of DLBCL patients

Overall, 1,057 patients receiving a primary treatment for DLBCL have been included in this analysis. More in detail, the median age was 61 years, the male sex was slightly more frequent (54%), and an IPI score > 2 was found in 39% of patients. A rituximab-containing regimen was given to 700 patients while 357 were not exposed to the antibody (Table I). We investigated the relationships between LMR and the most relevant clinical features measured at diagnosis. The cutoff point of LMR for survival outcomes was selected by the ROC curve analysis in the training set from the Bergamo series (data not shown). The most sensitive (70%) and specific (53%) cutoff value of LMR for survival was 2.6 in close accordance with an analogous LMR cutoff.
value recently reported by others [19]. Similarly, an AMC value $>0.62 \times 10^9/L$ and ALC value $<1.10 \times 10^9/L$ were equally associated with an adverse clinical presentation. We could confirm that patients with an LMR value $\leq 2.6$ were more frequently male ($P = 0.02$) and had an advanced Ann Arbor disease stage ($P = 0.002$) as well as a worst ECOG PS, a higher LDH level, and a higher IPI ($P = 0.000$). On the contrary, no statistical correlation was observed with age and the presence of extranodal sites (Table I). The association between a low LMR ($\leq 2.6$) and a high-risk clinical presentation was equally significant for patients receiving rituximab-supplemented chemotherapy and those receiving chemotherapy alone (Table I).

**Response to primary treatment according to LMR and IPI**

Overall, a higher proportion of complete remission (CR)/very good partial remission (VGPR) achievement was observed in patients receiving a rituximab-supplemented chemotherapy (86%) compared to patients treated with chemotherapy alone (81%; $P = 0.0381$). In both groups, a

| Table III. Harrell’s C-Statistic for Discriminatory Values on Survival |
|-----------------|-----------------|
| Patients treated without rituximab ($N = 357$) | Patients treated with rituximab ($N = 700$) |
| Harrell’s $C^a$ | Harrell’s $C^a$ |
| 95% CI | 95% CI |
| AMC | 0.4921 | 0.45–0.53 |
| ALC | 0.4727 | 0.43–0.52 |
| LMR | 0.5082 | 0.47–0.55 |

$^a$ C values range from 0.5 (absence of discrimination) to 1 (perfect discrimination). ALC, absolute lymphocyte count; AMC, absolute monocyte count; LMR, lymphocyte to monocyte ratio.

![Figure 1](image-url)
higher CR/VGPR achievement was observed in patients with low IPI scores compared to those with a high IPI scores (Table II). On the contrary, a low LMR was associated with poor response among patients receiving rituximab-supplemented chemotherapy, whereas no significant differences in the response rates between low and high LMR were observed among patients receiving chemotherapy alone (Table II). Similarly, response to first-line treatment was significantly associated to LMR ($P = 0.000$) only in patients receiving rituximab-supplemented chemotherapy, while IPI retained its relevance in both groups. Interestingly, the majority (75%) of primary refractory patients was associated to low LMR ($< 2.6$) only in the cohort receiving rituximab-supplemented chemotherapy.

**LMR at diagnosis predicts survival of DLBCL treated with rituximab-based chemotherapy**

We performed a Harrell's C-statistics analysis, that is the most appropriate tool to identify time-dependent, clinically relevant biologic prognostic factors, to investigate the discriminative impact on survival of the AMC, ALC, and LMR [25]. Interestingly, for patients treated with chemotherapy alone, none of these prognostic factors were found significant, while for patients receiving a rituximab-supplemented chemotherapy, Harrell's C values were significantly informative (Table III). Patients receiving rituximab-supplemented chemotherapy have been followed for a median of 40 months (range 2–140), whereas the median follow-up for patients receiving chemotherapy alone was 77 months (range 2–330). The OS was significantly higher in patients receiving rituximab-supplemented chemotherapy compared to those receiving chemotherapy alone, with 4-year projections of 79% and 59%, respectively ($P = 0.0000$; Supporting Information Fig. 1A). In the longer term, the OS was clearly influenced by the IPI score in both patient groups. Indeed, according to the IPI score, the 4-year OS of patients not exposed to rituximab, was 68% and 43%, as compared to 87% and 65% for patients receiving a rituximab-supplemented chemotherapy (Supporting Information Fig. 1B,C). The LMR did not identify patient subgroups with significantly different survival expectancy among patients receiving chemotherapy alone, with a 4-year OS of 61% and 56% for high and low LMR, respectively (Fig. 1A). On the other hand, the LMR value was highly predictive among patients receiving rituximab-supplemented chemotherapy, with a significantly poorer outcome for patients with low LMR (73% at 4 years) compared to those with LMR >2.6 (66% at 4 years) (Fig. 1B). The predictive value of LMR holds true for the EFS only in rituximab-exposed patients, whereas no significant differences were observed according to LMR in terms of DFS (Fig. 1C-F).

To further investigate the prognostic value of LMR, univariate and multivariate analyses were performed in the cohort treated with rituximab. Several factors were associated with poor outcome, including LMR value $< 2.6$ (Table IV). In multivariate analysis, both IPI scores $>2$ and LMR $< 2.6$ maintained a high association with poor outcome (Table V). Results from the multivariate analysis were strengthened by the Harrell’s C-index that strongly indicates the role of LMR as a biomarker significantly affecting survival in patients with DLBCL receiving a rituximab-supplemented chemotherapy program.

**Predictive value of LMR in R-CHOP-treated patients**

The analysis was then focused on the main subgroup of R-CHOP-treated patients. As mentioned, R-CHOP-treated patients had a markedly different survival according to IPI (89% and 63% at 4 years, for low and high IPI scores, respectively; Fig. 2A) as well as to LMR (86% and 72% at 4 years, for high and low LMR, respectively; Fig. 2B). The LMR was then assessed in the IPI subgroup. The LMR cut-off value of 2.6 allowed to identify distinct prognostic subgroups among patients with low IPI (93% and 83% at 4 years, for high and low LMR, respectively; Fig. 2C) as well as among patients with high IPI (70% and 60% at 4 years, for high and low LMR, respectively; Fig. 2D).

**Discussion**

The evaluation of the peripheral blood absolute LMR obtained at diagnosis by a standard automated complete blood count represents a novel and immediate prognosticator with an interesting biological relevance in DLBCL patients [18,19]. In this manuscript, we describe the prognostic impact of LMR in two large cohorts of DLBCL patients receiving chemotherapy with or without rituximab. By ROC curve analysis and Harrell’s C-statistics, we were able to confirm that LMR is an informative marker of clinical response and OS of DLBCL patients. Indeed, our findings underline that both lymphopenia and monocytosis are significant factors impacting prognosis. These results, while confirming those previously reported by other investigators, provide further innovative information. For the first time we provide evidence that at diagnosis a low LMR is strongly associated with high-risk clinical features but is prognostically relevant only for patients receiving a rituximab-based program. This observation underlines that the more aggressive is the biology of the lymphoma, the more compromised is the function of the immune system. Of note this is likely to be the case not only for DLBCL, but also for Hodgkin’s [29,30] and non-Hodgkin’s lymphomas of different histology [31]. The key role of the adaptive immune response to the developing lymphoma has been a long recognized and extensively investigated issue [7], but more recent results have clearly shown that via CCL5, lymphoma B cells can recruit monocytes which in turn support the survival and proliferation of neoplastic B cells [17] and suppress the proliferation of normal T cells [32].
Beyond the more aggressive clinical presentation, a low LMR at diagnosis was prognostically relevant only for patients receiving rituximab-supplemented chemotherapy. This observation strongly supports the role of the immune system in mediating the dramatic effect of rituximab, particularly for the achievement of a robust clinical response, and provides further information on the mechanism of action of rituximab, which encompass the induction of programmed cell death, complement-dependent cytotoxicity and most importantly an antibody-dependent cellular cytotoxicity (ADCC) [33–35]. In this respect, a reduction of the absolute number of lymphocytes may be obviously impacting ADCC by a simple reduction of the circulating effector cells. In addition, the ability of rituximab to change so remarkably the long-term outcome of B-cell lymphomas has led to the suggestion that it may mediate a long-lasting immunization effect due to the release of tumor antigens and changes in localized inflammation. In this context, it seems obviously important that variations of the immune microenvironment and particularly the absolute number of circulating lymphocytes might lead to a different ability of dendritic cells to uptake tumor-associated antigens, to cross-present them to T lymphocytes and to provide the potential for an active cell-mediated immunity [36]. On the other hand, lymphoma cells may directly drive the expansion of monocytes and macrophage subsets that can support tumor growth and hamper immune response [37]. Beyond the effect on tumor promotion, it is tempting to speculate whether monocytes may alter rituximab pharmacokinetics by accelerating its clearance, which has been shown to be a possible key factor to explain response heterogeneity of DLBCL [38].

The second important result of our study is the IPI-independent impact of LMR on the long-term survival of DLBCL patients treated with rituximab-supplemented chemotherapy. The robustness of our observation is based on the absolute number of patients who entered this analysis, the presence of non-rituximab-treated historical controls in whom this effect was not observed, and the type of analysis we performed. Indeed, the IPI-independent impact of LMR was documented not only by stratifying patients with a low or high IPI and according to LMR cutoff but also most importantly by using time-dependent Cox multivariable analysis and Harrell’s C-index. This latter in particular seems to be the most appropriate and accurate test to validate a biomarker with a possible impact on survival [25,26]. Although our results are in keeping with those reported by others, some obvious cautions should be considered. The retrospective nature of this analysis is the most important one although it is worth-noting that the training set of results obtained in one institution (Bergamo) was fully reproduced and validated by results obtained elsewhere (Turin, Milan, and Palermo). Nonetheless, a full validation of our observation requires a prospective analysis that has been already launched at several Italian centers. An additional limit is the lack of immunologic details as to the T cell and monocyte subset definition at diagnosis. In fact, while the simple automatic blood count definitely represents a crucial added value for its simplicity and obvious reproducibility, it would be clearly important to understand whether the proportion of different T cell or monocyte subpopulations at diagnosis could better illustrate and explain the biologic background of these results. In addition, the heterogeneity in treatment regimens, sample size (two-thirds of patients receiving rituximab-supplemented vs. one-third receiving chemotherapy alone), or yet unrecognized differences in patient populations may have contributed to the different prognostic value of LMR. Finally, at this time, we cannot provide major

Figure 2. OS according to (A) the International Prognostic Index (IPI) and (B) lymphocyte to monocyte ratio (LMR) in R-CHOP-treated patients. OS according to LMR in (C) IPI 0–2 or (D) IPI > 2 in R-CHOP-treated patients.
biologic details as to the heterogeneity of our patients such as the definition of an activated B-cell-like (ABC) or a germinal center B-cell-like (GCB) DLBCL molecular profile [39] nor the proportion of cases bearing multiple genetic hits (“double-hit lymphomas”) [40]. In fact, it remains a distinct possibility that distinct biologic signatures may finally repre-
sent the key element to define also the immunologic response and balance detectable in the peripheral blood of DLBCL at diagnosis. To underline the prognostic value of LMR, it should be noted that innovative treatments usually reduce the clinical impact of biological prognostic factors and this has been a common experience in the treatment of acute leukemias, particularly childhood acute lymphoblastic leukemia [41]. On the contrary, the striking clinical impact of LMR in patients treated with rituximab strongly emphasized the key role of a well-preserved immune system for achiev-
ing best clinical results in patients treated with immune chemotherapy.

Our results confirm and extend the notion that the evaluation of LMR at diagnosis is a simple and robust tool to better define clinical response and long-term survival of DLBCL patients receiving a modern, rituximab-supplemented chem-
otherapy. Prospective studies are needed to define whether LMR can help to define more appropriate treatments of patients identified for being at higher risk of a poor clinical outcome.

Author Contributions
A.Ra., A.M.G., and C.T. designed the study; A.Ra., G.G., and C.T. wrote the manuscript; F.D., A.Ro., A.M.B., D.C., M.L., A.D.C., L.D., and C.P. collected the data; C.B., F.D., E.O., R.P., and A.G. analyzed the data and performed the statistical analysis. All authors critically read and revised the manuscript.

References
1. Feugier P, Van Hoof A, Sebban C, et al. Long-term results of the R-CHOP study in the treatment of elderly patients with diffuse large B-cell lymphoma: A study by the Groupe d’Etude des Lymphomes de l’Adulte. J Clin Oncol 2005; 23:4117–4126.
2. Pfleurchschuhl M, Trümper L, Osterborg A, et al. CHOP-like chemotherapy plus rituximab versus CHOP-like chemotherapy alone in young patients with good-prognosis diffuse large-B-cell lymphoma: A randomised controlled trial by the MabThera International Trial (MInT) Group. Lancet Oncol 2006;7:379–391.
3. Sehn LH, Berry B, Chhanabhai M, et al. The revised International Prognostic Index (IPI) is a better predictor of outcome than the standard IPI for patients with diffuse large B-cell lymphoma treated with R-CHOP. Blood 2007;105:1857–1861.
4. Tarella C, Zanni M, Di Nicola M, et al. Prolonged survival in poor-risk diffuse large B-cell lymphoma following front-line treatment with rituximab-supplemented, early-intensified chemotherapy with multiple autologous hematopoietic stem cell support: A multicenter study by GITIL (Gruppo Italiano Terapie Innovative nei Linfomi). Leukemia 2007;21:1802–1811.
5. Alizadeh AA, Eisen MB, Davis RE, et al. Distinct types of diffuse large B-cell lymphoma identified by gene expression profiling. Nature 2000;403:503–511.
6. Xu-Monette ZY, Wu L, Visco C, et al. Mutational profile and prognostic significance of TP53 in diffuse large B-cell lymphoma patients treated with R-CHOP: Report from an International DLBCL Rituximab-CHOP Consortium Program Study. Blood 2012;120:3986–3996.
7. Lenz G, Wright G, Dave SS, et al. Stromal gene signatures in large-B-cell lymphomas. N Engl J Med 2008;359:2313–2323.
8. Coupland SE. The challenge of the microenvironment in B-cell lymphomas. Histopathology 2011;58:89–90.
9. Hans CP, Weisenburger DD, Greiner TC, et al. Confirmation of the molecular classification of diffuse large B-cell lymphoma by immunohistochemistry using a tissue microarray. Blood 2004;103:275–282.
10. Salles G, de Jong D, Xie W, et al. Prognostic significance of immunohistochemical biomarkers in diffuse large B-cell lymphoma: A study from the International Lymphoma Biomarker Consortium. Blood 2011;117:7070–7078.
11. Gutierrez-Garcia G, Cerdas-Salzmann T, Climent F, et al. Gene-expression profiling and not immunophenotypic algorithms predicts prognosis in patients with diffuse large B-cell lymphoma treated with immunotherapy. Blood 2011;117:4836–4843.
12. A predictive model for aggressive non-Hodgkin’s lymphoma. N Engl J Med 2005;352:987–994.
13. Ziepert M, Hasenclever D, Kühn E, et al. Standard International prognostic index remains a valid predictor of outcome for patients with aggressive CD20+ B-cell lymphoma in the rituximab era. J Clin Oncol 2010;28:2373–2380.
14. Steidl C, Lee T, Shah SP, et al. Tumor-associated macrophages and survival in classic Hodgkin’s lymphoma. N Engl J Med 2010;362:875–885.
15. Steidl C, Conners JM, Gascogne RD. Molecular pathogenesis of Hodgkin’s lymphoma: Increasing evidence of the importance of the microenvironment. J Clin Oncol 2011;29:1812–1826.
16. Behl D, Ristow K, Markovic SN, et al. Absolute lymphocyte count predicts therapeutic efficacy of rituximab therapy in follicular lymphomas. Br J Haema-
tol 2007;137:409–415.
17. Mueller CG, Boix C, Kwan W-H, et al. Critical role of monocytes to support normal B cell and diffuse large B cell lymphoma survival and proliferation. J 2286.
18. Li Z-M, Huang J-J, Xia Y, et al. Blood lymphocyte-to-monocyte ratio identifies high-risk patients in diffuse large B-cell lymphoma treated with R-CHOP. PLoS One 2012;7:e41568.
19. Wilcox RA, Ristow K, Habermann TM, et al. The absolute monocyte and lymphocyte prognostic score predicts survival and identifies high-risk patients in diffuse large-B-cell lymphoma. Leukemia 2011;25:1502–1509.
20. Fischer R, et al. Comparison of a standard regimen (CHOP) with three intensive chemotherapy regimens for advanced non-
Hodgkin’s lymphoma. N Engl J Med 1993:328:1002–1006.
21. Gianni AM, Bregni M, Siena S, et al. High-dose chemotherapy and autologous bone marrow transplantation compared with MACOP-B in aggressive B-cell lymphoma. N Engl J Med 1997;336:1290–1298.
22. Cheson BD, Horning SJ, Coffier B, et al. Report of an international workshop to standardize response criteria for non-Hodgkin’s lymphomas. NCI Sponsored International Working Group. J Clin Oncol 1999;17:1244.
23. Mantel H, Haenszel W. Statistical analysis of the data from retrospective studies of disease. J Natl Cancer Inst 1959;22:719–748.
24. Harrell FE, Jr, Lee KL, Mark DB. Multivariable prognostic models: Issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. Stat Med 1996;15:361–387.
25. Wang TJ, Gona P, Larson MG, et al. Multiple biomarkers for the prediction of first major cardiovascular events and death. N Engl J Med 2006;355:2631–2639.
26. Carabio B, Antonioni E, Guglielmelli P, et al. Leukocytosis and risk stratification: assessment in essential thrombocythemia. J Clin Oncol 2008;26:2732–2736.
27. Antonelli L, Borachia B, Biganzoli E. The ratio of the absolute lymphocyte count to the absolute monocyte count is associated with prognosis in Hodgkin’s lymphoma. Correlation with tumor-associated macrophages. Oncologist 2010;15;781–80.
28. Porrata LF, Ristow K, Habermann TM, et al. Peripheral blood lymphocyte/ monocyte ratio at diagnosis and survival in nodular lymphocyte-predominant Hodgkin lymphoma. Br J Haematol 2012;157:321–330.
29. Koh YW, Kang HJ, Park C, et al. The ratio of the absolute lymphocyte count to the absolute monocyte count is associated with prognosis in diffuse large B-cell lymphoma patients treated with R-CHOP. J Clin Oncol 2011;29:8788–8794.
30. Peto R. Asymptotically efficient rank invariant test procedures. J R Stat Soc 1972:135:185–206.
31. Lim SH, Beers SA, French RR, et al. Anti-CD20 monoclonal antibodies: Histological effects. Nat Med 2000;6:443–446.
32. Golay J, Lazzari M, Facchinetti V, et al. CD20 levels determine the in vitro susceptibility to rituximab and complement of B-cell chronic lymphocytic leukemia: First regulation by CD55 and CD59. Blood 2001;98:3383–3389.
33. Weiner GJ. Rituximab: Mechanism of action. Semin Hematol 2010;47:115–123.
34. Clynnes RA, Towers TL, Presta LG, Ravetch JV. Inhibitory Fc receptors modu-
late in vivo cytotoxicity against tumor targets. Nat Med 2000;6:443–446.
35. Golay J, Lazzari M, Facchinetti V, et al. CD20 levels determine the in vitro susceptibility to rituximab and complement of B-cell chronic lymphocytic leukemia: First regulation by CD55 and CD59. Blood 2001;98:3383–3389.
36. Nevin GJ. Rituximab: Mechanism of action. Semin Hematol 2010;47:115–123.