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Review Article

Importance of Relative Dose Intensity in Chemotherapy for Diffuse Large B-Cell Lymphoma

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CHOP therapy combined with rituximab (R-CHOP) is currently a standard chemotherapy for diffuse large B-cell lymphoma (DLBCL). However, relapse is detected despite R-CHOP in approximately 30% of patients. Treatment results should be further improved. Previously, second- and third-generation therapies such as MACOP-B, m-BACOD, and ProMACE-CytaBOM were performed to improve the results of DLBCL treatment. However, dose intensity (DI) enhancement increased treatment-associated toxicity, and the treatment results did not improve. Recently, the entity of the relative dose intensity (RDI) was proposed as an index of the intensity of chemotherapy. In this method, the ratio of actual DI to the DI designed per specific period is numerically evaluated. The purpose of calculating the RDI is to achieve chemotherapy as scheduled while maintaining the DI, and not to improve the DI. Previous studies reported that the maintenance of the RDI during CHOP therapy improved the treatment results. In this paper, we review DI and RDI in studies of DLBCL, and revisit the significance of these indicators.
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Keywords: diffuse large B-cell lymphoma, dose intensity, relative dose intensity, R-CHOP

INTRODUCTION

There is a correlation between the dose of anti-tumor drugs and their therapeutic effects. These effects are thought to be particularly dependent on the amount of drug administered per unit time. "Dose intensity (DI)", which represents the amount (mg/m^2) of a drug administered per unit time (week), is used to evaluate the intensity of chemotherapy. This indicator is used mainly for tumors that are relatively sensitive to anti-tumor drugs and has been widely used in the treatment of malignant lymphoma.

An indicator called "relative dose intensity (RDI)" has also been proposed.[1] RDI reflects whether the DI of a therapy was implemented as planned, and is now commonly included in reports of clinical studies. RDI is a useful indicator for evaluating the feasibility of a drug therapy at a given strength. Multiple reports have also demonstrated a correlation between RDI and survival prognosis.[2-8] Therefore, even in daily practice, RDI is an indicator that one should be aware of.

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In this paper, we review DI and RDI in studies of diffuse large B-cell lymphoma (DLBCL), and revisit the significance of these indicators.

INCREASE OF DOSE INTENSITY (DI) IN DLBCL THERAPIES

CHOP therapy (CHOP) is a combination chemotherapy of four drugs : cyclophosphamide (CPA), doxorubicin (ADM), vincristine (VCR), and prednisone (PSL). Although CHOP is a standard therapy for DLBCL, it has been unsuccessful in a substantial number of patients. Therefore, therapies superior to CHOP have been actively developed and studied. These therapies typically rely on increased DI.

Second- and third-generation chemotherapy regimens, such as m-BACOD, MACOP-B, and ProMACE-CytaBOM, were developed in the 1980s. These therapies involve many additional anti-cancer drugs. The third-generation chemotherapies attempt to increase DI by concentrating the administration of drugs in a short time period. Some excellent results were observed in phase II trials,[9-11] but third-generation therapies failed to show superiority to CHOP in a large-scale phase III trial.[12]

A new therapy called CHOP-14 was developed in the 1990s, partly because granulocyte colony-stimulating factor (G-CSF) became available. CHOP-14 increases DI by shortening its treatment interval from 21 days (CHOP-21) to 14 days. A study conducted by the German High-Grade Non-

Hodgkin's Lymphoma Study Group (DSHNHL) demonstrated the superiority of CHOP-14 to CHOP-21 in elderly patients.[13] This study compared four therapies : CHOP-14 and CHOP-21, as well as CHOEP-14 and CHOEP-21, which include etoposide. CHOP-14 was superior to CHOP-21 in complete remission rate, three-year event-free survival rate, and five-year overall survival rate. However, a similar study with young, low-risk patients showed that CHOEP-21 was superior.[14] Thus, the superiority of CHOP-14 is not yet clear.

In the 2000s, R-CHOP, which is CHOP in combination with rituximab, an anti-CD20 chimeric antibody, has become a standard therapy for initial presentation of DLBCL. The superiority of CHOP-14 to CHOP-21 has not been demonstrated in combination with rituximab. In the 2009 American Society of Hematology meeting, a preliminary report was presented on LNH-03-6B, an ongoing clinical trial conducted by Groupe d'Etude des Lymphomes de l'Adulte (GELA).[15] This trial compares the efficacy of R-CHOP-14 with R-CHOP-21 in elderly DLBCL patients. In the preliminary analysis of 202 patients, the two-year progression-free survival rates were 49% for the R-CHOP-14 group and 63% for the R-CHOP-21 group, thus showing no statistically significant difference at that time ($p = 0.1186$). We are looking forward to the results of the final analysis of 602 cases.

High-dose chemotherapy plus autologous hematopoietic stem cell transplantation (HDC + ASCT) has also been repeatedly explored as an approach to increase DI. However, similar to other chemotherapies with increased DI, the superiority of HDC + ASCT in its efficacy for treating initial presentation cases is currently unclear. Multiple clinical trials to test HDC + ASCT have been carried out. A typical example is the GOELAMS 072 trial that compared two therapies in patients younger than 60 years of age in the initial presentation stage of aggressive lymphoma.[16] Patients in the control group were treated eight times with standard CHOP. Patients in the test group were first treated with two rounds of CEEP (cyclophosphamide, epirubicin, vindesine, and prednisone) therapy. Those patients who exhibited better than partial response (PR) were then treated with MC (methotrexate and cytarabin) therapy, followed by HDC + ASCT. Within the high-intermediate risk group (HI) as defined by the International Prognostic Index (IPI), both the event-free survival rate (56% vs. 28% for test and control groups, respectively ; $p = 0.003$) and overall survival rate (74% vs. 44%, $p = 0.001$) were significantly higher for patients treated with HDC + ASCT. Another trial, GOELAMS 075, was a phase II trial that tested the efficacy of HDC + ASCT in combination with rituximab. It involved high-risk patients with initial presentation of DLBCL, and reported promising results.[17] We note, however, that many HDC + ASCT clinical trials had been conducted before the introduction of rituximab. Some studies have shown negative results for HDC + ASCT during the first remission of DLBCL in high-IPI-risk groups.[18,19] Currently there is no consensus on the efficacy of HDC + ASCT for initial presentation stages of DLBCL. Improvement in treatment results for DLBCL in high-risk patients is still hoped for even following the introduction of R-CHOP. The large-scale clinical trial S9704 is currently testing therapies with rituximab. Patients with a high risk of age-adjusted IPI are treated with eight rounds of R-CHOP or with six rounds of R-CHOP plus HDC + ASCT.

RELATIVE DOSE INTENSITY (RDI) IN DLBCL THERAPIES

RDI represents the ratio of the amount of a drug actually administered (actual DI) to the amount planned (planned DI) for a fixed time period (Fig. 1).[2] The purpose of calculating RDI is to evaluate whether or not the planned DI of a chemotherapy treatment was actually achieved.

RDI tends to remain satisfactory in most large-scale clinical trials. A typical example is the Mab Thera International Trial (MinT), in which young patients with low IPI risk scores were treated with a CHOP-like regimen either with or without rituximab. RDI was maintained at a median of 97% in both rituximab and non-rituximab groups.[20] The LNH 98-5 trial by GELA examined CHOP with and without rituximab in elderly patients. Although this trial did not use RDI as an indicator, at least 90% of the planned doses of CPA and ADM were administered for over 90% of the patients in both groups.[21] Other clinical trials of CHOP-like regimens have also shown well-maintained RDI,[22,23] suggesting that a high RDI in CHOP-like regimens is relatively easy to maintain in a clinical trial setting.

In routine medical practice, however, drug doses may be reduced or the timing of administration may be postponed for various reasons including a patient's advanced age, organ damage, or complications such as infections. When chemotherapy is conducted on an outpatient basis, treatment intervals may become longer than planned because of a patient's social factors or calendar conflicts. Because routine medical

First step : standard or reference DI of each drug separately

$$\frac{\text{Planned full dose of drug per cycle (mg/m}^2\text{)}}{\text{Planned number of weeks in cycle (week)}}$$

Second step : actual DI for each drug

$$\frac{\text{Total dose of drug actually received by the patient (mg/m}^2\text{)}}{\text{Total number of weeks actually needed to receive total dose (week)}}$$

Third step : RDI of each drug

$$\frac{\text{Actual DI of each drug}}{\text{Standard DI of each drug}} \text{ (fraction)}$$

Fourth step : average RDI of CHOP

$$\frac{\text{Sum of RDI CPA, ADM, and VCR}}{3} \text{ (fraction)}$$

Fig. 1. Relative dose intensity calculation
DI, dose intensity ; RDI, relative dose intensity ; CHOP, cyclophosphamide (CPA), doxorubicin (ADM), vincristine (VCR), and prednisone

practice involves certain elements that are not envisioned in clinical trials, it is not necessarily easy to maintain a high RDI. Lyman *et al*. conducted a large-scale investigation of CHOP-like regimens performed in routine practice at 567 institutions in the US (4,513 cases).[24] The results showed that the average RDI was approximately 80%. In 53% of the cases, an RDI of 85% or better could not be maintained. In 40% of the cases, the amount of drugs administered was reduced by at least 15%, and in 24% of the cases, the administration of drugs was delayed for 7 days or longer. The same report showed that with the progression of treatment cycles, an increasing number of cases failed to maintain an RDI of 85% or better. Among elderly patients in particular, the number of cases in which an RDI of 85% could not be maintained started to increase at early cycles.

RELATIONSHIP BETWEEN RDI AND SURVIVAL PROGNOSIS

It has been pointed out that maintenance of RDI is related to survival prognosis. Epelbaum *et al*. found that in CHOP treatment of patients with stage III-IV DLBCL, the prognosis deteriorated significantly when RDI of CPA fell below 70%.[2] Kwak *et al*. examined the relationship between prognosis and RDI of various drugs in 115 DLBCL patients treated by CHOP, m-BACOD, or MACOP-B therapies. Significantly worse prognoses were reported for cases with less than 75% RDI of ADM.[4] Table 1 shows a summary of the reports describing studies of the importance of maintaining RDI in CHOP. In every report, cases with a decreased RDI were found to have significantly deteriorated prognoses.

The above studies were conducted without rituximab. It is unclear whether maintenance of RDI in chemotherapy is important even in combination with rituximab. Recently, we examined the relationship between RDI and survival prognosis in 152 incipient DLBCL cases, all treated by CHOP-like regimens in combination with rituximab.[25] For cases in which an average RDI (ARDI) of 70% could not be maintained, progression-free survival (PFS) (ARDI$\geq$70% vs. ARDI$<$70% : 83.7 and 63.6%, respectively, $p = 0.003$) and overall survival (OS) (ARDI$\geq$70% vs. ARDI$<$70% : 97.1 and 81.1%, respectively, $p = 0.005$) decreased significantly. The same data were further analyzed for two separate groups : patients classified (by IPI) as low and low-intermediate (L-LI group), and patients classified as high and high-intermediate (H-HI group). While a decline in ARDI did not appear to affect prognosis in the L-LI group (ARDI$\geq$70% vs. ARDI$<$70% : PFS : 91.9 and 81.1%, respectively, $p = 0.288$, OS : 100 and 90.2%, respectively, $p = 0.250$), an inability to maintain ARDI at or above 70% resulted in a significant prognostic deterioration in the H-HI group (ARDI$\geq$70% vs. ARDI$<$70% : PFS : 75.1 and 47.2%, respectively, $p = 0.002$, OS : 94.1 and 71.1%, respectively, $p = 0.008$). These results suggest the interesting possibility that the H-HI group may include more cases with a larger amount of tumors than the L-LI group, which may

Table 1. Summary of retrospective analyses reporting a relationship between survival and relative dose intensity (RDI) in diffuse large B-cell lymphoma (DLBCL)

Authors	Year of publication	No. of patients	Treatment regimen	Cutoff of RDI	Adverse outcome for low RDI group
Epelbaum R, *et al*.[2]	1988	78	CHOP	CPA : 70% initial ARDI	OS
Epelbaum R, *et al*.[3]	1990	95	CHOP	(CPA, ADM, CPA) : median	OS
Kwak LW, *et al*.[4]	1990	118	CHOP, m-BACOD, MACOP-B	ADM : 75%	OS
Lepage E, *et al*.[5]	1993	311	ACVB	ARDI (CPA, ADM) : 70%	OS
Bosly A, *et al*.[6]	2008	348	CHOP, ACVBP, CHVmP-BV	ARDI (all drugs) : 90%	OS
Pettengell R, *et al*.[7]	2008	78	CHOP	ARDI (all drugs) : 90%	OS
Terada Y, *et al*.[8]	2009	100	R-CHOP	ARDI (CPA, ADM) : per 10%	OS
Hirakawa *et al*.[25]	2010	152	R-CHOP, R-THP-COP	ARDI (CPA, ADM/THP-ADM, VCR, PSL) : 70%	OS, PFS

DI, dose intensity ; RDI, relative dose intensity ; CHOP, cyclophosphamide (CPA), doxorubicin (ADM), vincristine (VCR), and prednisone ; R-CHO, CHOP therapy combined with rituximab

explain why RDI maintenance has a greater impact on the H-HI group.

FACTORS AFFECTING RDI

As described above, however, routine practice involves different conditions than clinical trials, and maintaining a high RDI is not easy in daily practice. It is therefore important to understand the factors that may affect RDI prior to starting chemotherapy.

According to a large-scale investigation carried out by Lyman et al. in the US, several factors tend to lower RDI : age (over 60 years), disease stage (stage III or later), and a performance status (PS) of two or greater.[24] The factor that mitigates these RDI-lowering risks is the administration of prophylactic G-CSF. A study that we conducted included analysis of the following RDI-lowering factors : age (over 60 years), THP-COP therapy with rituximab (R-THP-COP), and febrile neutropenia (FN).[25] THP-COP therapy involves CHOP-like regimens and is applied for elderly persons in Japan.[26] In this regimen, tetrahydropyranyl adriamycin (THP-ADM), which exhibits reduced cardiac toxicity, was used instead of ADM, and the doses of CPA and VCR were decreased. Prophylactic use of G-CSF mitigates these risks of RDI reduction. Taken together, these results suggest that administration of prophylactic G-CSF might be useful in daily practice for maintaining a high RDI when treating a DLBCL patient with the above risk factor(s).

The American Society of Clinical Oncology (ASCO) recommends primary use of prophylactic G-CSF for patients with a risk of developing FN of 20% or higher, and secondary use of prophylactic G-CSF for patients who experience complications accompanying neutropenia (such as FN from a prior cycle of chemotherapy), and for whom a dose reduction in the next cycle may compromise the prognosis.[27] Even when the risk of developing FN due to the therapy itself is less than 20%, the guidelines recommend that prophylactic use of G-CSF is appropriate for patients with an increased risk of developing FN for other reasons, such as advanced age (65 or older), past history of FN, or unfavorable performance status. A meta-analysis also showed that prophylactic G-CSF significantly lowers the risk not only of developing FN, but also of early death including infection-related death.[28] Use of prophylactic G-CSF should be considered for cases with an increased risk of developing FN to lower the risk of early death as well as to maintain a high RDI.

CONCLUSION

R-CHOP has improved treatment results for patients in initial presentation of DLBCL. Among high-risk patients, however, further improvement is necessary. We hope to see the development of therapies with increased DI for the high-risk group, by means of stratifying and isolating high-risk cases using IPI or other categorizations. Even in combination with rituximab, patients with lowered RDI have an unsatisfactory prognosis. For patients at risk of RDI decline, it is important to implement measures, such as prophylactic use of G-CSF, in order to minimize the decline in RDI.

REFERENCES

1 Hryniuk W, Bush H: The importance of dose intensity in chemotherapy of metastatic breast cancer. J Clin Oncol 2:1281-1288, 1984

2 Epelbaum R, Haim N, Ben-Shahar M, Ron Y, Cohen Y: Dose-intensity analysis for CHOP chemotherapy in diffuse aggressive large cell lymphoma. Israel J Med Sci 24:533-538, 1988

3 Epelbaum R, Faraggi D, Ben-Arie Y, Ben-Shahar M, Haim N, *et al.* : Survival of diffuse large cell lymphoma. A multivariate analysis including dose intensity variables. Cancer 66:1124-1129, 1990

4 Kwak LW, Halpern J, Olshen RA, Horning SJ: Prognostic significance of actual dose intensity in diffuse large-cell lymphoma: results of a tree-structured survival analysis. J Clin Oncol 8:963-977, 1990

5 Lepage E, Gisselbrecht C, Haioun C, Sebban C, Tilly H, *et al.* : Prognostic significance of received relative dose intensity in non-Hodgkin's lymphoma patients: application to LNH-87 protocol. The GELA. (Groupe d'Etude des Lymphomes de l'Adulte). Ann Oncol 4:651-656, 1993

6 Bosly A, Bron D, Van Hoof A, De Bock R, Berneman Z, *et al.* : Achievement of optimal average relative dose intensity and correlation with survival in diffuse large B-cell lymphoma patients treated with CHOP. Ann Hematol 87:277-283, 2008

7 Pettengell R, Schwenkglenks M, Bosly A: Association of reduced relative dose intensity and survival in lymphoma patients receiving CHOP-21 chemotherapy. Ann Hematol 87:429-430, 2008

8 Terada Y, Nakamae H, Aimoto R, Kanashima H, Sakamoto E, *et al.* : Impact of relative dose intensity (RDI) in CHOP combined with rituximab (R-CHOP) on survival in diffuse large B-cell lymphoma. J Exp Clin Cancer Res 28:116, 2009

9 Gordon LI, Harrington D, Andersen J, Colgan J, Glick J, *et al.* : Comparison of a second-generation combination chemotherapeutic regimen (m-BACOD) with a standard regimen (CHOP) for advanced diffuse non-Hodgkin's lymphoma. N Engl J Med 327:1342-1349, 1992

10 Klimo P, Connors JM: MACOP-B chemotherapy for the treatment of diffuse large-cell lymphoma. Ann Intern Med 102:596-602, 1985

11 Longo DL, DeVita VT Jr., Duffey PL, Wesley MN, Ihde DC, *et al.* : Superiority of ProMACE-CytaBOM over ProMACE-MOPP in the treatment of advanced diffuse aggressive lymphoma: results of a prospective randomized trial. J Clin Oncol 9:25-38, 1991

12 Fisher RI, Gaynor ER, Dahlberg S, Oken MM, Grogan TM, *et al.* : Comparison of a standard regimen (CHOP) with three intensive

chemotherapy regimens for advanced non-Hodgkin's lymphoma. N Engl J Med 328:1002-1006, 1993

13 Pfreundschuh M, Trümper L, Kloess M, Schmits R, Feller AC, *et al.*: Two-weekly or 3-weekly CHOP chemotherapy with or without etoposide for the treatment of elderly patients with aggressive lymphomas: results of the NHL-B2 trial of the DSHNHL. Blood 104:634-641, 2004

14 Pfreundschuh M, Trümper L, Kloess M, Schmits R, Feller AC, *et al.*: Two-weekly or 3-weekly CHOP chemotherapy with or without etoposide for the treatment of young patients with good-prognosis (normal LDH) aggressive lymphomas: results of the NHL-B1 trial of the DSHNHL. Blood 104:626-633, 2004

15 Delarue R, Tilly H, Salles G, Gisselbrecht C, Mounier N, *et al.*: R-CHOP14 compared to R-CHOP21 in elderly patients with diffuse large B-cell lymphoma: results of the interim analysis of the LNH03-6B GELA study. Blood 114:169, 2009 (Abstract)

16 Milpied N, Deconinck E, Gaillard F, Delwail V, Foussard C, *et al.*: Initial treatment of aggressive lymphoma with high-dose chemotherapy and autologous stem-cell support. N Engl J Med 350:1287-1295, 2004

17 Dilhuydy MS, Lamy T, Foussard C, Gressin R, Casassus P, *et al.*: Front-line high-dose chemotherapy with rituximab showed excellent long-term survival in adults with aggressive large B-cell lymphoma: final results of a phase II GOELAMS study. Biol Blood Marrow Transplant 16:672-677, 2010

18 Gisselbrecht C, Lepage E, Molina T, Quesnel B, Fillet G, *et al.*: Shortened first-line high-dose chemotherapy for patients with poor-prognosis aggressive lymphoma. J Clin Oncol 20:2472-2479, 2002

19 Kaiser U, Uebelacker I, Abel U, Birkmann J, Trümper L, *et al.*: Randomized study to evaluate the use of high-dose therapy as part of primary treatment for "aggressive" lymphoma. J Clin Oncol 20:4413-4419, 2002

20 Pfreundschuh M, Trümper L, Osterborg A, Pettengell R, Trneny M, *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 7:379-391, 2006

21 Coiffier B, Lepage E, Briere J, Herbrecht R, Tilly H, *et al.*: CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large-B-cell lymphoma. N Engl J Med 346:235-242, 2002

22 Doorduijn JK, van der Holt B, van Imhoff GW, van der Hem KG, Kramer MH, *et al.*: CHOP compared with CHOP plus granulocyte colony-stimulating factor in elderly patients with aggressive non-Hodgkin's lymphoma. J Clin Oncol 21:3041-3050, 2003

23 Osby E, Hagberg H, Kvaløy S, Teerenhovi L, Anderson H, *et al.*: CHOP is superior to CNOP in elderly patients with aggressive lymphoma while outcome is unaffected by filgrastim treatment: results of a Nordic Lymphoma Group randomized trial. Blood 101:3840-3848, 2003

24 Lyman GH, Dale DC, Friedberg J, Crawford J, Fisher RI: Incidence and predictors of low chemotherapy dose-intensity in aggressive non-Hodgkin's lymphoma: a nationwide study. J Clin Oncol 22:4302-4311, 2004

25 Hirakawa T, Yamaguchi H, Yokose N, Gomi S, Inokuchi K, *et al.*: Importance of maintaining the relative dose intensity of CHOP-like regimens combined with rituximab in patients with diffuse large B-cell lymphoma. Ann Hematol 89:897-904, 2010

26 Tsurumi H, Hara T, Goto N, Kanemura N, Kasahara S, *et al.*: A phase II study of a THP-COP regimen for the treatment of elderly patients aged 70 years or older with diffuse large B-cell lymphoma. Hematol Oncol 25:107-114, 2007

27 Smith TJ, Khatcheressian J, Lyman GH, Ozer H, Armitage JO, *et al.*: 2006 update of recommendations for the use of white blood cell growth factors: an evidence-based clinical practice guideline. J Clin Oncol 24:3187-3205, 2006

28 Kuderer NM, Dale DC, Crawford J, Lyman GH: Impact of primary prophylaxis with granulocyte colony-stimulating factor on febrile neutropenia and mortality in adult cancer patients receiving chemotherapy: a systematic review. J Clin Oncol 25:3158-3167, 2007