 IMPORTANCE OF RELATIVE DOSE INTENSITY IN CHEMOTHERAPY FOR DIFFUSE LARGE B-CELL LYMPHOMA

Hiroki Yamaguchi, Tsuneaki Hirakawa, and Koiti Inokuchi

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.

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/m²) 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. 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. Therefore, even in daily practice, RDI is an indicator that one should be aware of.

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, but third-generation therapies failed to show superiority to CHOP in a large-scale phase III trial.

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-

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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 chemotherapy regimens 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. 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, etoposide, vincristine, and prednisone) therapy. Those patients who exhibited better than partial response (PR) were then treated with MC (methotrexate and cytarabine) 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. 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. 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). 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. 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. Other clinical trials of CHOP-like regimens have also shown well-maintained RDI, 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 practice often requires dose modifications, RDI tends to remain satisfactory in most large-scale clinical trials.
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). 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%. 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. 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. For cases in which an average RDI (ARDI) of 70% could not be maintained, progression-free survival (PFS) (ARDI ≥ 70% vs. ARDI < 70%: 83.7 and 63.6%, respectively, p = 0.003) and overall survival (OS) (ARDI ≥ 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 ≥ 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 ≥ 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)

<table>
<thead>
<tr>
<th>Authors</th>
<th>Year of publication</th>
<th>No. of patients</th>
<th>Treatment regimen</th>
<th>Cutoff of RDI</th>
<th>Adverse outcome for low RDI group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epelbaum R, et al.2</td>
<td>1988</td>
<td>78</td>
<td>CHOP</td>
<td>CPA: 70% initial ARDI</td>
<td>OS</td>
</tr>
<tr>
<td>Epelbaum R, et al.3</td>
<td>1990</td>
<td>95</td>
<td>CHOP</td>
<td>CPA, ADM, CPA: median</td>
<td>OS</td>
</tr>
<tr>
<td>Kwak LW, et al.4</td>
<td>1990</td>
<td>118</td>
<td>CHOP</td>
<td>ADM: 75%</td>
<td>OS</td>
</tr>
<tr>
<td>Lepage E, et al.3</td>
<td>1993</td>
<td>311</td>
<td>ACVB</td>
<td>ARDI (CPA, ADM): 70%</td>
<td>OS</td>
</tr>
<tr>
<td>Bussel A, et al.5</td>
<td>2008</td>
<td>348</td>
<td>CHOP</td>
<td>ARDI (all drugs): 90%</td>
<td>OS</td>
</tr>
<tr>
<td>Pettengell R, et al.7</td>
<td>2008</td>
<td>78</td>
<td>CHOP</td>
<td>ARDI (all drugs): 90%</td>
<td>OS</td>
</tr>
<tr>
<td>Terada Y, et al.8</td>
<td>2009</td>
<td>100</td>
<td>R-CHOP</td>
<td>ARDI (CPA, ADM): per 10%</td>
<td>OS</td>
</tr>
<tr>
<td>Hirakawa et al.25</td>
<td>2010</td>
<td>152</td>
<td>R-CHOP, R-THP-COP</td>
<td>ARDI (CPA, VCR, PSL): 70%</td>
<td>OS, PFS</td>
</tr>
</tbody>
</table>

DI, dose intensity; RDI, relative dose intensity; CHOP, cyclophosphamide (CPA), doxorubicin (ADM), vincristine (VCR), and prednisone; R-CHO, CHOP therapy combined with rituximab
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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. 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). 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 to lower the risk of early death as well as to maintain a high RDI.

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.

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