The Prednisone Dosage in the CHOP Chemotherapy Regimen for Non-Hodgkin’s Lymphomas (NHL): Is There a Standard?

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Key Words. Prednisone · CHOP · NHL · Survey

Abstract

Purpose. Discrepancies in the quoted prednisone dosages in the regimens reported as the only standard CHOP regimen stimulated our interest in reviewing the medical literature regarding this issue and to assess whether practicing hematologists and oncologists in the U.S. are aware of the different dose schedules of prednisone in the published CHOP programs.

Methods. Sixteen textbooks and chemotherapy reference books were reviewed. A MEDLINE search of English-language articles published between January 1970 and December 1998 was performed. An eight-point questionnaire was sent via e-mail with responses obtained from 421 hematology/oncology physicians in the U.S.

Results. Sixteen textbooks and chemotherapy reference books reviewed quoted only one prednisone dosage as part of the standard CHOP regimen; the prednisone dosages quoted as standard varied between publications. More than 4,000 eligible non-Hodgkin’s lymphoma patients have been treated with the CHOP chemotherapy as part of 43 different clinical trials reviewed. The dosages of prednisone and prednisolone used varied among six different levels. Thirty percent (127/421) of practicing U.S. physicians were not aware of the existence of more than one prednisone dose schedule as part of the CHOP regimen. The three most frequently used dosages are 100 mg/days 1-5 (67%), 100 mg/m²/days 1-5 (17%), and 60 mg/m²/days 1-5 (13%).

Conclusions. Discrepancies in steroid dosages used as part of the reported standard CHOP regimens are common and not well recognized in the medical literature nor by practicing U.S. hematologists/oncologists. Based on this study, a prednisone dose of 100 mg/day for five days should be considered the standard dose. The Oncologist 2000;5:238-249

Background

Over the last two decades, the incidence of non-Hodgkin’s lymphoma (NHL) has increased in the U.S. at a rate of 4% per year [1, 2]. Estimates from the American Cancer Society indicate that this year there will be over 56,800 new cases of NHL diagnosed in the U.S. alone and almost half that number will die of this disease, making NHL the seventh most common cause of death from cancer in the U.S. [3]. The CHOP (cyclophosphamide, hydroxydaunomycin [doxorubicin], oncovin [vincristine], and prednisone) chemotherapy regimen has become the gold standard for the treatment of NHL. Discrepancies in the quoted prednisone dosages in the regimens reported as the only standard CHOP regimen in several hematology/oncology textbooks stimulated our interest in reviewing the medical literature regarding this issue. We were also interested in evaluating whether practicing hematologists and oncologists in the U.S. were aware of the different dose schedules of prednisone in the published CHOP programs, and to assess which steroid dosages they were using as part of the CHOP chemotherapy regimen for the treatment of NHL.

Methods

A MEDLINE search of English-language articles published between January 1970 and December 1998 was conducted, using the terms CHOP and non-Hodgkin’s lymphoma or NHL. Original articles reporting the results of treatments of patients with NHL treated with CHOP alone in at
least one arm of the study or with CHOP and growth factor support were selected. Only trials with a minimum of 20 eligible patients were included. Trials where CHOP regimens were given in a different schedule than every three-four weeks or where patients received in the same given cycle other chemotherapy agents besides CHOP were excluded, as well as articles reporting the four-drug combination with other names than CHOP. Bibliographies, book chapters, some original protocols, and meetings abstracts were reviewed for additional relevant information. Text and tables with the recommended CHOP chemotherapy regimen from 13 major textbooks of hematology and oncology and three chemotherapy reference books were reviewed. Relevant data on patient population, tumor histology and staging, response rate, overall survival, and disease-free survival were extracted and analyzed. The material was classified into six different treatment categories according to the dosages of prednisone used in each study. Response rates were extracted as originally reported in each article. Survival data could not be analyzed in view of the differences in reported follow-up periods.

An eight-point questionnaire was sent via e-mail. The targeted group of U.S. physicians were those whose names and e-mail addresses were listed in the 1999 American Society of Clinical Oncology’s (ASCO) directory book and who had listed their primary specialty as “medical oncology” and/or “hematology.” Permission was obtained from the membership and publication departments of ASCO for this e-mail survey. The Mayo Clinic’s Institutional Review Board (IRB #418-99) approved this national survey before we proceeded with it and the Mayo Foundation provided the appropriate funding.

**RESULTS**

**Review of Hematology and Oncology Textbooks and Chemotherapy Reference Books**

Thirteen textbooks of hematology and oncology and three chemotherapy reference books were reviewed [4-19]. As shown in Table 1, three different dose levels of prednisone are quoted by different references as the standard dose: 100 mg/day (12 references), 100 mg/m²/day (3 references), and 50 mg/m²/day (1 reference), each for five consecutive days. None of these references mention that there is more than one prednisone dose schedule in previously reported CHOP regimens.

**MEDLINE Search Results**

More than 4,000 eligible NHL patients have been treated with the CHOP chemotherapy as part of 43 different clinical trials identified that met the above criteria. Most patients formed part of trials aimed to treat patients with advanced disease (Ann Arbor stage I-II: 1,696 patients; stage III-IV: 2,584 patients) and with intermediate/high-grade NHL (3,783 patients). The dosages of prednisone and prednisolone vary among six different levels, as summarized below.

**The First CHOP Combination**

Gottlieb et al. [20] from the M.D. Anderson Cancer Center, conducted a phase I clinical trial, where single agent adriamycin was compared to a combination of doxorubicin (ADR), cytosine-arabinoside (ARA-C), vincristine (VCR), and prednisone (Pred) (Combination 1) and to a combination of cyclophosphamide, doxorubicin, vincristine, and prednisone (Combination 2: CTX 600 mg/m²/day 1, ADR 40 mg/m²/day 1, VCR 1.4 mg/m²/day 1, and prednisone 100 mg/m²/day 1-5). This is the first published article with the combination of this four-drug regimen that represents the CHOP chemotherapy regimen, although the dosages of these drugs were different from the trial that followed (SWOG 7204). The Eastern Cooperative Oncology Group (ECOG) and the Cancer and Leukemia Group B (CALGB), however, have always used this higher dose of prednisone in their CHOP trials. We should note that when this chemotherapy combination was first published as a preliminary report in an abstract form in Clinical Research in 1972 [21], the dosages quoted for this combination were cyclophosphamide 600-900...
mg/m²/day 1, doxorubicin 40-60 mg/m²/day 1, vincristine 2 mg/day 1, and prednisone 200 mg per day for five days.

**Level I: Prednisone 100 mg/day/days 1-5**

Approximately 2,493 patients with NHL were treated with CHOP using a prednisone dose of 100 mg/day/days 1-5 as part of 21 different clinical trials. Two of the largest trials using this dose level are discussed below.

The excellent results obtained in a previous pilot study by Gottlieb et al. [20] led to the first large, prospective, randomized trial (SWOG trial 7204), using the CHOP chemotherapy regimen for NHL (CTX 750 mg/m²/day 1, doxorubicin 40-60 mg/m²/day 1, vincristine 2 mg/day 1, and prednisone 100 mg/days 1-5 [25 mg po four times daily]), conducted between April 1972 and September 1974 [22]. This is the study that most textbooks and published clinical trials using the CHOP program refer to as the source for the standard CHOP regimen and the first trial that uses the name CHOP to identify this chemotherapy combination. Five hundred and six patients with stage III and IV NHL were entered in this study. Patients were randomly assigned between CHOP (246 eligible patients/204 evaluable patients) and HOP (ADR, VCR, and prednisone); patients in complete remission after consolidation chemotherapy were then randomized to a maintenance chemotherapy program with either COP (CTX, VCR, and prednisone) or OAP (VCR, ARA-C, and prednisone).

One of the most important prospective clinical trials for patients with NHL was the national high-priority lymphoma study (Intergroup 0067; SWOG 8516; ECOG 3487) conducted between April 4, 1986, and June 15, 1991 [23]. In this study, 1,138 previously untreated patients with advanced disease were registered and 899 were found eligible. CHOP regimen with prednisone at 100 mg/day/days 1-5 (225 patients) was compared with the newer and more aggressive chemotherapy regimens known as m-BACOD (methotrexate, bleomycin, doxorubicin, cyclophosphamide, vincristine, and dexamethasone), ProMace-CyaBOM (prednisone, methotrexate, doxorubicin, cyclophosphamide, etoposide, cytarabine, and bleomycin), and MACOP-B (methotrexate, doxorubicin, cyclophosphamide, vincristine, bleomycin and prednisone). There has been no statistically significant difference in overall response rate, time to treatment failure, or overall survival among these four regimens. The CHOP regimen proved to be less toxic and less expensive. This study established CHOP as the gold standard for the treatment of NHL, and the regimen used as the benchmark for all new treatments.

The comparative analyses of these and the remainder of clinical trials using a CHOP regimen with prednisone at 100 mg daily for five days are summarized in Table 2.

**Level II: Prednisone 100 mg/m²/day/days 1-5**

One of the largest trials using this dose of prednisone was the ECOG 6483/CALGB 8694 trial [43], conducted from July 1984 through January 1988 and comparing the second-generation chemotherapeutic regimen m-BACOD with the “standard CHOP.” A total of 392 patients with Ann Arbor stage III-IV intermediate/high-grade lymphoma were enrolled, 325 of whom were found eligible. One hundred and seventy-four of these patients received treatment with the CHOP program. The CHOP regimen in this trial was developed from the COPA regimen, a four-drug regimen (cyclophosphamide 600 mg/m²/day 1, oncovin 1.4 mg/m²/day 1, prednisone 100 mg/m²/days 1-5, and Adriamycin [doxorubicin] 50 mg/m²/day 1) developed by ECOG and tested in the ECOG 3474 [44] and ECOG 5477 trials [45]. In the original E6483 protocol [46] the investigators remark, “The combination COPA has been chosen as a control arm because of its demonstrated activity in previous ECOG studies. However, we have elected to employ Cyclophosphamide at a dose level of 750 mg/m² (rather than 600 mg/m² as in our previous studies). This dose level has been shown by others [24] to be well-tolerated.”

Other clinical trials using this dose of prednisone are reviewed in Table 3.

**Level III: Prednisone 75 mg/m²/day/days 1-5**

Two Canadian studies have reported using this dosage of prednisone. Meyer et al. [51] (June 1990 to February 1993) published their results of a randomized trial comparing “standard CHOP” with weekly CHOP in 38 elderly patients with bulky stage II, stage III-IV, or any stage with positive B symptoms and intermediate grade NHL. Connors et al. [52] (May 1980 to December 1984) treated 78 consecutive patients with stage I-II aggressive NHL with three cycles of CHOP followed by involved field radiation (Table 3).

**Level IV: Prednisone 60 mg/m²/day/days 1-5**

The PETHEMA group (Programa para el Estudio y la Terapéutica de las Hemopatías Malignas) conducted a phase III trial comparing CHOP (76 patients) versus ProMace-CyaBOM in 148 eligible patients with stages II-IV intermediate and high-grade NHL [53]. Another prospective randomized study conducted at Memorial Sloan-Kettering Cancer Center using six cycles of adjuvant CHOP after radiation therapy for pathologic stage I low and intermediate grade NHL also used a prednisone dose of 60 mg/m²/day (Table 3) [54].

**Level V: Prednisone 50 mg/m²/day/days 1-5 (or days 1-8)**

Nine different clinical trials have been identified using prednisone at this dose level. Most of these trials were done in Europe or Asia. In the U.S., the division of oncology at
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Stanford University published one of the very first trials with this dose. This study was conducted from June 1974 to May 1977 with 23 patients with diffuse histiocytic lymphoma. The treatment program was noted to be “as previously described by Coltman et al.” [61]. The Novantrone (mitoxantrone) International Study Group, which conglomerated 14 countries in four different continents, ran a phase III study (7/84 to 10/87) comparing CHOP versus CN(novantrone)OP in 359 previously untreated patients with intermediate and high-grade NHL, stage II-IV. A total of 159 patients out of 263 eligible patients received CHOP [56]. Between November 1987 and October 1992, the British National Lymphoma Investigation (BNLI) group conducted a randomized comparison of PACE-BOM (Prednisone, ADR, CTX, VP 16, Bleomycin, VCR, and Methotrexate) versus “standard regimen” CHOP in patients with aggressive NHL. From a total of 459 eligible patients, 226 received CHOP with a prednisolone dose of 50 mg/m²/days 1-8. Although this CHOP regimen differs from the American programs, the authors acknowledged the difference and noted that this is the regimen that the BNLI was using since 1974 [55]. The results of other randomized clinical trials using this steroid dosage and conducted by the Lymphoma Group of Central Sweden [62], the Swedish Lymphoma Study Group [56], the European Organization for Research and Treatment of Cancer Lymphoma Cooperative Study Group [59], the Dutch Hemato-Oncology Study Group [58], and by the Grupo Argentino de Tratamiento de la Leucemia Aguda and Grupo Latinoamericano de Tratamiento de Hemopaties Malignas [63] are noted in Table 3.

### Level VI: Prednisone 40 mg/m²/day/days 1-5

This level of steroid has been used mainly outside the U.S.. Only one of those published studies was a prospective randomized study where CHOP was compared to MEVP (mitoxantrone, etoposide, vindesine, and prednisolone) for treatment of intermediate-grade and high-grade NHL (Table 3) [63].

An additional single trial using a prednisone dosage of 60 mg daily for five days [66] was found but was not included for final analysis.

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**Table 2. Clinical trials reported using CHOP as one of the treatment arms with prednisone dose at level I (100 mg/day for five days)**

<table>
<thead>
<tr>
<th>Study</th>
<th>n of Patients All/eligible</th>
<th>CHOP n of Patients</th>
<th>Histology (n)</th>
<th>Ann Arbor Stage (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>L.G.¹</td>
<td>I/H.G.²</td>
</tr>
<tr>
<td>McKelvey [22]</td>
<td>506/506</td>
<td>246</td>
<td>148</td>
<td>262</td>
</tr>
<tr>
<td>Jones [23]</td>
<td>774/715</td>
<td>252</td>
<td>281</td>
<td>388</td>
</tr>
<tr>
<td>Cooper² [25]</td>
<td>304/236</td>
<td>111</td>
<td>—</td>
<td>236</td>
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<tr>
<td>Verdonk [27]</td>
<td>320/286</td>
<td>286</td>
<td>—</td>
<td>286</td>
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<tr>
<td>Gottlieb [28]</td>
<td>413/274</td>
<td>141</td>
<td>—</td>
<td>274</td>
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<tr>
<td>Miller [29]</td>
<td>401/401</td>
<td>401</td>
<td>—</td>
<td>401</td>
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<tr>
<td>Tondini [31]</td>
<td>183/183</td>
<td>183</td>
<td>—</td>
<td>183</td>
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<tr>
<td>Armitage [32]</td>
<td>75/75</td>
<td>75</td>
<td>—</td>
<td>75</td>
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<tr>
<td>Cohen [33]</td>
<td>90/90</td>
<td>90</td>
<td>—</td>
<td>90</td>
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<tr>
<td>Matthews³ [34]</td>
<td>80/80</td>
<td>33</td>
<td>—</td>
<td>80</td>
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<tr>
<td>Meurers [35]</td>
<td>63/63</td>
<td>26</td>
<td>63</td>
<td>—</td>
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<tr>
<td>Gerhardt [36]</td>
<td>61/61</td>
<td>34</td>
<td>—</td>
<td>61</td>
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<td>Andersen [37]</td>
<td>206/85</td>
<td>44</td>
<td>NA</td>
<td>NA</td>
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<td>Gomez [38]</td>
<td>26/26</td>
<td>26</td>
<td>—</td>
<td>26</td>
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<tr>
<td>Hovgaard [39]</td>
<td>32/32</td>
<td>32</td>
<td>6</td>
<td>26</td>
</tr>
<tr>
<td>Epelbaum [40]</td>
<td>28/28</td>
<td>28</td>
<td>—</td>
<td>28</td>
</tr>
<tr>
<td>Okabe [41]</td>
<td>40/40</td>
<td>20</td>
<td>—</td>
<td>40</td>
</tr>
</tbody>
</table>

¹L.G. = Low grade and “favorable” histology.
²I/H.G = Intermediate/high grade and “unfavorable” histology.
³Prednisolone 100 mg/po/days 1-5.
⁴CTX 600 mg/m²/i.v./day 1, ADR 50 mg/m²/i.v./day 1, VCR 1 mg/m²/i.v./day 1, prednisone 100 mg/po/days 1-5.
RESPOSTE RATES

Intermediate and High-Grade non-Hodgkin’s Lymphoma

Early Stage

More than 1,600 patients with Ann Arbor stage I-II have been treated with CHOP alone or with CHOP and radiation therapy as part of 30 clinical trials (Tables 2 and 3). When analyzing patients treated with CHOP alone and receiving the two most frequently used dose levels of prednisone (levels I and II; Table 4), the mean complete response rates are 77.5% and 74.5% for levels I and II, respectively.

Advanced Stage

The largest group of patients treated with CHOP has been the one with advanced stage NHL. Approximately 35
clinical trials have been conducted using all six different levels of prednisone. When analyzing trials with a minimum of 50 Ann Arbor stage III and IV patients treated with at least six cycles of CHOP, the mean complete response rates are 54.75% and 54.5% for prednisone levels I and II, respectively (Table 4).

Table 5 shows the complete response rates and their calculated 95% confidence intervals for response rate data collected from trials that used CHOP for advanced aggressive NHL.

Survey

The eight-point questionnaire was sent via e-mail to 3,125 U.S. physicians from the 1999 ASCO directory book who met the selection criteria. The selection criteria used were unable to discern between physicians currently in clinical practice and taking care of NHL patients from those who did not. Six hundred and twenty-four (20%) e-mail messages were returned as “undeliverable mail.” The major reasons were invalid e-mail addresses due to typographical errors in the directory and physicians changing e-mail addresses or no longer working for the institutions that own those e-mail addresses. Of the 2,501 physicians that we suspect have received the survey, 610 of them (24.4%) responded to the survey. One hundred and eighty-nine (7.5%) of them did not answer the questionnaire. Most frequent reasons cited for not answering were that they were not involved in the care of NHL patients, that they have already retired from active practice, or that they were involved in administrative or research activities at different biotechnology and pharmaceutical companies. Four hundred and twenty-one physicians completed the questionnaire.

Fifty-one percent (214/421) of physicians who responded to the survey have cared for more than 10 new cases of NHL in 1998 and 63% of them (263/421) treated at least five patients with CHOP during the same year. Thirty percent (127/421) of these practicing physicians were not aware of the existence of more than one prednisone dose schedule as part of the CHOP regimen. The three most frequent dosages being used are 100 mg/days 1-5 (67%), 100 mg/m²/days 1-5 (17%)
<table>
<thead>
<tr>
<th>Dose Level</th>
<th>Study - CHOP for NHL of Aggressive Histology</th>
<th>CI (95%)</th>
<th>50% CR</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td><em>McKelvey</em> [22]</td>
<td>CHOP until CR, then additional CHOP × 3</td>
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<td></td>
<td><em>Jones</em> [23]</td>
<td>CHOP × 8</td>
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<td></td>
<td><em>Fisher</em> [24]</td>
<td>CHOP × 8</td>
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<td></td>
<td><em>Cooper</em> [25]</td>
<td>CHOP × 8</td>
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<td></td>
<td><em>Gams</em> [26]</td>
<td>CHOP × 8</td>
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<td><em>Verdonk</em> [27]</td>
<td>CHOP × 8</td>
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<td><em>Armitage</em> [32]</td>
<td>CHOP × 8</td>
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<td><em>Cohen</em> [33]</td>
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<td><em>Gerhartz</em> [36]</td>
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<td><em>Gomez</em> [38]</td>
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<td><em>Okabe</em> [41]</td>
<td>CHOP × 8</td>
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<td></td>
<td><em>Meyer</em> [42]</td>
<td>CHOP × 8</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td><em>Gordon</em> [43]</td>
<td>CHOP × 2 → Response → CHOP × 6</td>
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<tr>
<td></td>
<td><em>Bezwoda</em> [45]</td>
<td>CHOP × 2 post-CR (minimum × 6)</td>
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<tr>
<td>III</td>
<td><em>Meyer</em> [48]</td>
<td>CHOP × 6</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td><em>Montserrat</em> [50]</td>
<td>CHOP × 2 post-CR (minimum × 6)</td>
<td></td>
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<tr>
<td>V</td>
<td><em>Linch</em> [52]</td>
<td>CHOP × 2 post-CR (minimum × 6)</td>
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<td></td>
<td><em>Bezwoda</em> [53]</td>
<td>CHOP × 2 post-CR (min. × 6/max. × 8)</td>
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<td><em>Hagberg</em> [54]</td>
<td>CHOP × 9 (minimum)</td>
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<td></td>
<td><em>Sonneveld</em> [55]</td>
<td>CHOP × 6-8</td>
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<td><em>Tirelli</em> [56]</td>
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<tr>
<td>VI</td>
<td><em>Tagaki</em> [60]</td>
<td>CHOP up to 10 cycles</td>
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<td></td>
<td><em>Schaafsma</em> [61]</td>
<td>CHOP up to 10 cycles</td>
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</table>
and 60 mg/m² days 1-5 (13%). Seventy-eight percent (330/421) write the prednisone dosage from “memory.” Forty-seven percent declared that they observe a clinically significant incidence of steroid-related adverse events and 80% of them thought that these occur in more than 5% of the cases (26% considered it to affect more than 20% of treated patients). Hyperglycemia, weight gain, psychosis/depression, edema, and gastric intolerance are felt to occur in ≥20% of the time by 32%, 23%, 20%, 19%, and 15% of the surveyed physicians, respectively. A subset analysis of the 47% of physicians who responded that they observe a clinically significant incidence of steroid-related adverse events failed to reveal a direct correlation between adverse events and dose of steroid used.

**DISCUSSION**

Steroids are an integral part of most regimens against lymphoproliferative disorders. In the 1940s, studies with the then recently purified adrenotropic hormone and adrenal cortical hormone, showed the ability of steroids to decrease the normal and malignant lymphoid tissues of mice [67-69]. In the early 1950s the first reports of the effect of steroids in lymphoid tissue were published and large dose steroid therapy was initially used for the management of advanced stage lymphomas and leukemias [70, 71]. In 1961 Rosenberg et al. reported a complete review of 1,269 cases of lymphosarcomas, and among them there was an approximately 8.9% partial response rate in 158 patients who were treated with ACTH (adrenocorticotropic hormone) or adrenal steroids [72]. The next year, Kofman et al. reported objective regression of lymphomas in 53% of patients with the use of prednisone at dose schedules of 100 to 200 mg per day [73].

Kyle et al. reviewed the results of 44 patients with malignant lymphoproliferative diseases treated with prednisone or prednisolone with dosages ranging from 50 to 150 mg daily for two to four weeks [74]. Peripheral lymphadenopathy decreased in 35 of 37 patients; splenomegaly was reduced in 27 of 29 patients; hemoglobin and platelet counts improved in 41 of 44 patients and 23 of 26 patients, respectively. Improvement of symptoms related to the lymphomas was seen in all patients. However, the benefit seen initially with the large dose of steroids could be sustained only by prolonging the treatment with a maintenance dose.

CHOP is still considered the gold standard treatment for intermediate and high-grade NHL, and is the most commonly used regimen for this disease. Discrepancies in steroid dosages used as part of the reported standard CHOP regimens are common and not well recognized in the medical literature. Although Table 4 may suggest similar response rates for intermediate/high-grade NHL treated with different prednisone dose schedules, we acknowledge that such a conclusion is probably unreachable from the current medical literature. A meta-analysis of these trials will not be able to analyze this data since these studies were conducted over a period of almost three decades, and during this time the histologic classification of lymphomas underwent several revisions as did the definition of response rates among the different studies. Also, the advent of more technologically advanced ancillary methods of diagnosis and the identification of prognostic factors have redefined the diagnosis and staging of patients with NHL. In Tables 2 and 3 we demonstrate that these CHOP regimens sometimes utilized not only different dosages of steroids, but also different dose schedules of the other chemotherapy agents. These changes should also be considered when analyzing the different outcomes. The reported response rates (with 95% confidence interval) and the number of patients in each study treated with CHOP for advanced aggressive NHL, is plotted in Table 5. From this figure we conclude that variations in the dose of prednisone used does not seem to significantly change the response rate in patients with NHL. Based on this table and the above discussion we have left the final conclusions regarding any relationship between the different dosages of steroids and response rates to the interpretation of the reader.

Several of our surveyed physicians questioned the real role of the steroids in the CHOP regimen for NHL. An interesting observation is that ABVD (ADR, bleomycin, vinblastine, and dacarbazine), the current gold standard regimen for the treatment of Hodgkin lymphomas, does not include steroids. Contrary to the belief that the “standard” dose of steroids in the CHOP regimen is well known by most physicians, our survey demonstrated that a third of practicing hematologist and oncologist across the country were not aware of the discrepancies existing in the medical literature regarding the dose of prednisone in the CHOP regimen and that the steroid dosages currently being used vary widely from a “low dose” of 1 mg/kg/days 1-5 to the “high-dose schedule” of 100 mg/m²/days 1-5. Most of the reviewed CHOP clinical trials limit the toxicities reported to those typically seen with the cytotoxic agents, namely, myelosuppression, infections, cardiac effects, and treatment associated mortality. Adverse effects such as memory disturbances, mood changes, insomnia, gastritis, new onset of arterial hypertension or diabetes mellitus, steroid-related withdrawal syndrome, steroid myopathy, and incidence of osteoporosis are rarely described, although it is well known that these side effects are relatively frequent in patients taking large doses of steroids. The Boston Collaborative Drug Surveillance Program reported an 11.4% incidence of acute adverse reactions among 718 consecutively monitored hospitalized medical patients receiving a mean dose of 32.2 mg of prednisone per day [75]. Gastrointestinal symptoms were the most common acute reactions...
seen with the use of steroids. A striking correlation of acute psychiatric reactions with the dose of prednisone received was also found (incidence of 1.3% for patients receiving 40 mg/day, 4.6% for those receiving 41-80 mg/day, and 18.4% for those taking 80 mg/day or more). Forty percent of all the patients in this study were treated for neoplastic diseases. Stizia et al. studied the side effects of CHOP in the treatment of NHL [76]. This 75-item self-report questionnaire showed that difficulty sleeping, feeling depressed, and weight gain occurred at an incidence of 56%, 45%, and 55%, respectively. These adverse effects are commonly seen with patients taking high doses of steroids. Nearly half of our surveyed physicians consider that their patients have to deal with clinically significant steroids-related side effects during their treatment with CHOP. Although some may argue that a 25% response rate to our survey was low, it is actually considered a good response by those currently conducting surveys via the internet. It must also be considered that a significant percentage of these e-mails were, for technical reasons, never delivered. Additionally, it was not targeted specifically to physicians whose practices are mostly limited to the treatment of lymphomas. However, more than half of the surveyed physicians has seen more than 10 NHL patients the prior year.

We believe that a prospective randomized trial will be able to answer these two important questions, “Does it make any difference what prednisone dose is utilized?” and “Can we spare our patients of the short- and long-term side effects of high-dose steroids without sacrificing the effectiveness of the CHOP regimen?” A trial comparing the two most common prednisone dosages used in the U.S. (100 mg/day for five days versus 100 mg/m²/day for five days) may prove that there are clinically significant differences in the efficacy and toxicities of these steroid dosages. Until such a study is performed and based on this retrospective review, a prednisone dose of 100 mg/day for five days should be considered the standard dose as part of the CHOP regimen. This dose is the most frequently reported, most referenced, and, based on this retrospective review, does not seem to be associated with a worse outcome than that seen in patients with intermediate/high-grade NHL treated with alternative prednisone dose schedules.

ACKNOWLEDGMENT

The authors wish to acknowledge the contributions of our colleagues—members of ASCO who took time from their busy schedules to answer our survey. We also wish to express our gratitude to Peter O’Brien, Ph.D. (Biostatistics, Mayo Clinic, Rochester, Minnesota) for his invaluable statistical assistance in the writing of this manuscript.

This study was supported by the Mayo Foundation, IRB #: 418-99 (approved May 1999).

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