# R-CHOP-14 IN PATIENTS WITH DIFFUSE LARGE-B-CELL LYMPHOMA (DLBCL) YOUNGER THAN 70 YEARS: A MULTICENTER AND PROSPECTIVE STUDY

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## ABSTRACT

**Background:** Several studies have shown that the addition of rituximab (R) to CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone), or shortening the interval between cycles of chemotherapy to two weeks, improves survival of patients with DLBCL.

These studies prompted our group (GOTEL) to evaluate the feasibility and efficacy of R-CHOP-14 in patients (pts) with DLBCL in a prospective study.

**Methods:** Patients (younger than 70 years, Pts) with stage bulky II, III or IV DLBCL, and no significant co-morbidities were included in the study. R was administered on day 1 before chemotherapy. R-CHOP was recycled every 14 days. No antimicrobial prophylaxis was administered. All pts received filgrastim (5 µg/kg) from day +3 to +10. Pts received 6 cycles if CR was achieved after 3 cycles; those in PR and those pts with bone marrow disease at diagnosis received 8 cycles. Involved field radiation therapy was permitted for pts with stage bulky II disease.

**Results:** From May 2002 to August 2004, 77 pts were included. Median age was 54 years (range, 15-70); 55 patients were younger than 60 years. According to the age adjusted International Prognostic Index (aaIPI), 13 pts (17%) had low risk disease, 27 pts (35%) low-intermediate risk, 29 pts (38%) high-intermediate risk, and 8 pts (10%) high risk disease.

Grade 3-4 toxicity occurred as follow: neutropenia in 15 pts (19%), anemia in 7 pts (9%), thrombocytopenia in 4 pts (5%), mucositis in 4 pts (5%) and peripheral neurotoxicity in 4 pts (5%).

Ten pts were hospitalized (febrile neutropenia: 8 cases, 1 case of gastric perforation and 1 pulmonary embolism).

After therapy, 61 pts (79%) achieved a CR/CRu (C.I. 95%: 57%-90%) and 14 pts (18%) a PR. 2 pts (3%) had refractory disease. With a median follow-up of 20 months, progression-free and overall survival at 24 months were 68% and 87%, respectively.

**Conclusion:** Administration of R-CHOP-14 (with filgrastim support) is feasible and effective in patients younger than 70 years.

## BACKGROUND

In the last four years, we have witnessed significant advances in the treatment of diffuse large-B-cell lymphoma (DLBCL). First, it was reported that the addition of rituximab (R) to CHOP chemotherapy (cyclophosphamide, doxorubicin, vincristine, prednisone) increased survival in patients over 60 years (Coiffier B et al, N Engl J Med 2002; 346: 235) and in patients under 60 years and good prognosis (Pfreundschuh M et al; Lancet Oncol 2006; 7: 379). Simultaneously, we knew the results of 2 German randomized trials that indicated that administration of CHOP every 14 days Increased survival in patients over and under 60 years (Pfreundschuh M et al; Blood 2004; 104: 626 and Blood 2004; 104: 634).

In May 2002, the Spanish Group for Treatment and Study of Lymphomas (GOTEL) initiated a prospective study to assess the prognostic value of circulating levels of several angiogenic factors in patients with DLBCL treated with R-CHOP. In the light of the advances in the treatment of DLBCL that had been reported up to now, our group decided to treat patients under 70 years, who were enrolled in this study with the R-CHOP schedule repeated every 14 days.

In the present poster, the course of the 80 patients under 70 years treated with R-CHOP/14, who were enrolled within the prospective study, is reported. The results were up-dated in April 2006.

## OBJECTIVE

- The objective of the prospective substudy in patients under 70 years was to assess efficacy and toxicity of the administration of the R-CHOP schedule every 14 days in patients under 70 years with diffuse large-B-cell lymphoma.

## METHODS

### Inclusion criteria

- Histologic diagnosis of DLBCL-B or any of its variants according to the WHO classification.
- Age between 18 and 70 years.
- Ann Arbor stage: bulky II, III or IV.
- CD 20 positive.
- Not having received previous treatment.
- Adequate kidney, liver and bone marrow function.
- Absence of severe heart disease.
- Negative HIV serology.
- Absence of serious active infection.
- Absence of known allergic reactions to murine proteins or to any component of the medication to be used.

### Treatment strategy

- R-CHOP/14:
  - Rituximab 375 mg/m2 i.v., day 1.
  - Cyclophosphamide 750 mg/m2 i.v., day 1.
  - Adriamycin 50 mg/m2 i.v., day 1.
  - Vincristine 1.4 mg/m2 (max, 2 mg) i.v., day 1.
  - Filgrastim 5 µg/kg s.c., days 4 to 10.
- Re-cycled every 14 days.
- No antibiotic prophylaxis was administered.
- Blood tests were made only on day 1 of every course.
- Six cycles were administered in patients without involvement of bone marrow and they achieved completed remission (CR) after the 3rd course.
- Patients with involvement of bone marrow or partial remission (PR) after the 3rd course received 8 cycles.
- Administration of complementary radiotherapy to patients with stage bulky II was allowed.
- No prophylaxis of the central nervous system was administered.

## RESULTS

### Characteristics of the patients

| | | | |
|---|---|---|---|
| **Age:** | | **Extranodal sites** | |
| median | 53 years | 0 | 31 (39%) |
| range | (18-70) | 1 | 25 (31%) |
| **Sex** | | 2 | 19 (24%) |
| Male | 47 p. (59%) | ≥3 | 5 (6%) |
| Female | 33 p. (41%) | **Bulky disease** | |
| **Stage** | | Yes | 51 (64%) |
| bulky II | 36 p. (45%) | No | 29 (36%) |
| III | 16 p. (20%) | **ECOG** | |
| IV | 28 p. (35%) | 0 | 38 (47%) |
| **B symptoms** | | 1 | 23 (29%) |
| Yes | 34 p. (43%) | 2 | 13 (18%) |
| No | 46 p. (57%) | 3 | 5 (6%) |
| **Bone marrow disease** | | **Age adjusted IPI** | |
| Yes | 15 p. (19%) | Low risk | 13 (16%) |
| No | 65 p. (81%) | Low-intermediate risk | 31 (39%) |
| | | High-intermediate risk | 27 (34%) |
| | | High risk | 9 (11%) |

### Treatment compliance

- Number of cycles administered:
  - Median 7 cycles.
  - 6 cycles 28 p. (35%).
  - 7 cycles 10 p. (12.5%).
  - 8 cycles 35 p. (44%).
- Only 7 patients (9%) received less than 6 cycles of R-CHOP/14:
  - 2 for early progressive disease.
  - 5 for toxicity.
- Relative dose Intensity (%):
  - Cyclophosphamide 90 % (22-100%).
  - Adriamycin 90 % (22-100%).
- Complementary radiotherapy on bulky disease:
  - 23 patients (29%).

### Grade 3-4 toxicity

| | | | |
|---|---|---|---|
| **Vomits** | | **Anemia** | |
| Grade 3 | 2 p. (2,5%) | Grade 3 | 5 (6,5 %) |
| Grade 4 | 2 p. (2,5%) | Grade 4 | 2 (2,5%) |
| **Mucositis** | | **Thrombopenia** | |
| Grade 3 | 4 p. (5%) | Grade 3 | 3 (4%) |
| **Neurotoxicity** | | Grade 4 | 1 (1%) |
| Grade 3 | 4 p. (5%) | **Neutropenia** | |
| **Liver toxicity** | | Grade 3 | 6 (7,5%) |
| Grade 4 | 1 p. (1%) | Grade 4 | 9 (11%) |
| **Kidney toxicity** | | **Rituximab infusional toxicity** | |
| Grade 3 | 1 p. (1%) | Grade 3 hypotension | 1 p. (1%) |
| **Infections** | | Grade 4 anaphylaxis | 1 p. (1%) |
| Grade 3 | 4 p. (5%) | Grade 3 bronchospam | 1 p. (1%) |
| Grade 4 | 9 p. (11%) | | |

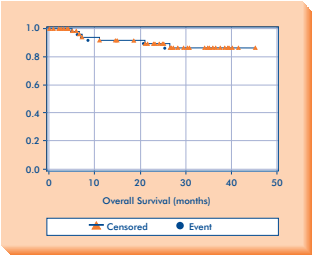
### Efficacy

- Median follow-up:
  - 26 months (range 1-46).
- Responses (77 evaluable patients):
  - CR-CRu: 61 p. (76%; 95% CI: 55-90%).
  - PR: 17 p. (21.5%; 95% CI: 16-35%).
  - 2 patients progressed during the treatment.
- Relapses:
  - 20 patients progressed or relapsed.
- Deaths (11 patients):
  - Progressive disease 9 p. (11%).
  - Toxicity: 1 p. (1%).
  - Not related to lymphoma (in CR) 1 p. (1%).

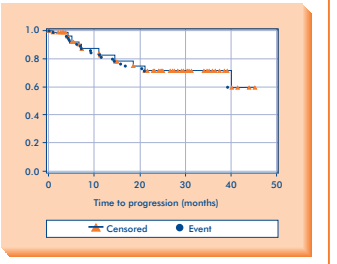
### Actuarial survival at 30 months

- Progression-free survival:
  - All patients(80 p.): 72%.
  - aaIPI 0/1 (44 p.): 84%.
  - aaIPI 2/3 (36 p.): 62%.
- Overall survival:
  - All patients (80 p.): 86%.
  - aaIPI 0/1 (44 p.): 91%.
  - aaIPI 2/3 (36 p.): 81%.

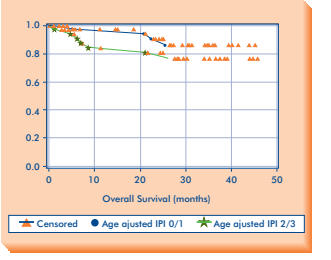
### Overall survival (all patients)



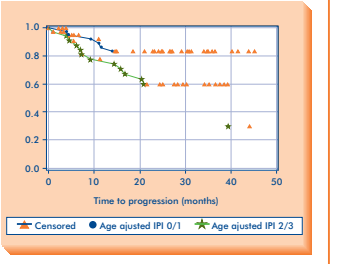

### Progression-free survival (all patients)




### Overall survival for aaIPI groups




### Progression-free survival for aaIPI groups




## CONCLUSIONS

- Administration of R-CHOP-14 (with filgrastim support) is feasible and effective in patients younger than 70 years.
- The intensity of the dose administered in this study is less than that recently reported in the RICOVER-60 study (90% versus 96%) (Pfreundschuh M et al; Blood 2005: 106; abstract 13), possibly due to the use of fewer days of filgrastim.
- It is necessary to compare R-CHOP/14 vs. R-CHOP/21 in all the risk groups.