



ORIGINAL ARTICLE

Gem-(R)CHOP versus (R)CHOP: a randomized phase II study of gemcitabine combined with (R)CHOP in untreated aggressive non-Hodgkin's lymphoma – EORTC lymphoma group protocol 20021 (EudraCT number 2004-004635-54)

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Abstract

Background: Despite recent improvements, many patients with aggressive non-Hodgkin's lymphoma (NHL) ultimately succumb to their disease. Therefore, improvements in front-line chemotherapy of aggressive NHL are needed. Gemcitabine is active in lymphoma. **Methods:** We performed a randomized phase II trial of the addition of gemcitabine to standard CHOP chemotherapy with or without rituximab [(R)CHOP]. The trial was also designed to determine the maximal tolerated dose (MTD) of gemcitabine in this combination. Patients with previously untreated aggressive NHL were randomized to receive either eight cycles of (R)CHOP given every 3 wk or (R)CHOP combined with gemcitabine [Gem-(R)CHOP]. **Results:** Twenty-five patients were enrolled in the trial before early closure. Twelve were randomized to Gem-(R)CHOP and 13 to (R)CHOP. MTD of gemcitabine was 800 mg/m² given on days 1 and 8; dose-limiting toxicity was hematologic. Five patients (42%) treated with Gem-(R)CHOP achieved complete response in comparison with 10 (77%) treated with (R)CHOP. Median time to treatment failure was 1.5 yr for Gem-(R)CHOP and 3.1 yr for (R)CHOP. Three patients receiving Gem-(R)CHOP had serious pulmonary toxicity, when compared to none receiving (R)CHOP. One patient died of pneumonitis. **Conclusions:** In this group of patients, addition of gemcitabine did not seem to improve outcomes. Gem-(R)CHOP in previously untreated patients with aggressive NHL occasionally results in severe, potentially fatal, pulmonary toxicity.

Key words antineoplastic protocols; gemcitabine; lymphoma, large B-cell; lymphoma large-cell, anaplastic; lymphoma non-Hodgkin; lymphoma, T cell, peripheral

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CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) given every 3 wk has been the backbone of front-line treatment of aggressive non-Hodgkin lymphomas (NHLs) for decades. Treatment with CHOP results in cure of 40–50% of patients with diffuse large B-cell lymphoma (DLBCL) but < 30% with peripheral T-cell lymphomas (PTCL) (1). The addition of rituximab (R)

increases the cure rate of DLBCL to about 60% (2). No such improvement has been achieved with PTCL. Attempts to improve the outcome of patients with aggressive NHL have been going on for decades but only lately have large randomized trials shown that the results of CHOP might be improved by the addition of other cytotoxic drugs, like etoposide (CHOEP) (3).

Gemcitabine is a pyrimidine antimetabolite that, after intracellular phosphorylation, inhibits ribonucleotide reductase and stops DNA strand elongation during replication (4, 5). It is widely used for treatment of solid tumors. Multiple phase II studies have reported good results with gemcitabine as a single agent or in combination for salvage treatment of lymphomas (6–14). Its main toxicity is hematologic. Two studies in previously untreated patients with Hodgkin's lymphoma (HL) have been stopped early because of unexpected severe pulmonary toxicity which was explained by a synergistic toxic effect of the combination of bleomycin and gemcitabine (15, 16).

Based on these data, we hypothesized that the addition of gemcitabine to standard CHOP might result in improved outcomes in patients with newly diagnosed aggressive NHL, while increasing only hematologic toxicity. We therefore initiated a randomized phase II trial of the combination of gemcitabine with CHOP (Gem-CHOP) in patients with previously untreated aggressive NHL. The objective of the trial was to determine the response rate, feasibility, and toxicity of the treatment. Because the maximal tolerated dose (MTD) of gemcitabine in this setting was unknown, an interim analysis of safety was foreseen to decide whether the combination was feasible and whether the initial dose of gemcitabine could be increased. At the time of study initiation, rituximab was not considered part of standard front-line treatment for DLBCL. Patients were therefore initially randomized between Gem-CHOP and CHOP. When it became clear that the addition of rituximab improves survival of patients with DLBCL, the protocol was amended and patients with B-NHL were randomized between Gem-R-CHOP and R-CHOP.

Patients and methods

Patients

Patients 18- to 70-yr old with previously untreated aggressive NHL stage II–IV and at least one bidimensionally measurable tumor mass, without significant comorbidity, central nervous system involvement, or known HIV positivity were eligible for the trial. After serious pulmonary toxicity was noted, only patients with normal pulmonary function tests were included, unless the reduction in FEV₁ or CO-diffusion capacity was because of lymphoma.

Treatment

All patients received standard CHOP chemotherapy every 3 wk. After the interim analysis, those with B-NHL also received rituximab 375 mg/m² per cycle. Patients achieving at least partial remission (PR) after

three cycles continued treatment for another five cycles, for a total of eight.

In the experimental arm, treatment with gemcitabine was initiated at a dose of 800 mg/m² over 30 min on days 1 and 8 of each cycle. Prior to the interim analysis, the dose was increased to 1000 mg/m² in patients without significant hematologic toxicity after three cycles. A possibility of further increasing the dose to 1250 mg/m² was foreseen. After the protocol was amended because of pulmonary toxicity, a course of prednisone 100 mg daily was given on days 8–10, together with the second gemcitabine dose.

Involved-field radiotherapy to regions with initially bulky disease or in PR after therapy was allowed and was not considered treatment failure.

Evaluations

Lymphoma staging and restaging was performed according to the previous version of the international working group recommendations and was based on CT criteria (17). In patients on treatment, blood counts were performed weekly and biochemical analyses at the beginning of each cycle. Pulmonary function tests and left-ventricle ejection fraction determination were performed prior to treatment start and after cycles 3 and 8. After the lethal pulmonary complication, the frequency of pulmonary function testing in the Gem-(R)CHOP arm was increased to every two cycles.

Endpoints and statistical considerations

The primary endpoint of the study was complete response (CR) rate, defined as either complete remission or complete remission unconfirmed according to standard criteria (17). Secondary endpoints were toxicity, feasibility, and freedom from treatment failure. Toxicity was graded using the Common Toxicity Criteria version 2.0 (<http://ctep.cancer.gov/reporting/ctc.html>). Treatment was considered feasible if at least 70% of cycles could be administered on time and at full dose. Freedom from treatment failure was defined according to standard criteria (17). All analyses were performed on an intention-to-treat basis.

The trial was originally planned as an open-label randomized phase II trial (one stage Fleming design) including 80 patients, testing the null hypothesis that the CR rate to Gem-CHOP is at least 50% (P₀ = 50%). The alternative hypothesis was that the CR rate was at least 70% (P₁ = 70%). A total of 38 patients were needed in each arm. After the addition of rituximab, the values of P₀ and P₁ in the statistical design were increased to 60% and 80%, respectively, with a total of 33 patients with DLBCL required in each arm of the trial. Patients were

centrally randomized using a minimization technique stratifying by institution, international prognostic index, and cell type. An interim safety analysis was foreseen after full treatment of at least six patients with Gem-CHOP or after the 10th patient had received at least three cycles, whichever occurred first. Early closure of the trial was foreseen in case of two deaths because of a similar unexpected cause.

Because this was a phase II trial, formal statistical comparisons between the two treatment arms were neither planned nor performed.

Ethical considerations

The trial was conducted in accordance with the Helsinki declaration, EU guidelines and laws and regulations of involved countries. The protocol was approved by the Lymphoma Group and the Protocol Review Committee (PRC) of the European Organization for Research and Treatment of Cancer (EORTC), as well as by PRCs, Ethical Committees and, where necessary, responsible administrative bodies of involved centers and countries.

Results

Patients' characteristics

Twenty-five patients were enrolled in the trial, 15 in the dose-finding part and ten in the second part before early closure because of low accrual (Table 1).

One of the patients from the CHOP arm was ineligible because of lack of measurable disease. This patient was taken off-study before administration of treatment because of neurological symptoms that occurred prior to treatment start.

MTD and toxicity

MTD of gemcitabine given together with CHOP was 800 mg/m² on days 1 and 8. The dose-limiting toxicity was hematologic. Neutropenia and thrombocytopenia causing dose reductions occurred in all patients in whom the dose of gemcitabine was increased to 1000 mg/m² after the third cycle.

Number of patients with adverse events grade 3 and 4 are given in Table 2. As expected, hematologic toxicity seemed more pronounced in the Gem-(R)CHOP arm. Serious pulmonary toxicity occurred in three patients treated with Gem-CHOP during the first part of the trial. Two had grade 3 dyspnea with FEV-1 or CO-diffusion reductions. One, with a large mediastinal tumor, developed pneumonitis after the second cycle and died because of respiratory failure. Autopsy findings were consistent with drug-induced diffuse alveolar damage. Exacerba-

Table 1 Patients' characteristics and outcomes

	Treatment		Total (n = 25) n (%)
	(R)CHOP (n = 13) n (%)	Gem-(R)CHOP (n = 12) n (%)	
Age (yr)			
Median	50	50	50
Range	25–70	34–61	25–70
Gender			
Male	7 (54)	6 (50)	13 (52)
Female	6 (46)	6 (50)	12 (48)
Performance status: (WHO)			
0–1	9 (69)	6 (50)	15 (60)
2–3	4 (31)	6 (50)	10 (40)
Clinical Ann Arbor stage			
II	5 (38)	3 (25.0)	8 (32)
III–IV	8 (62)	9 (75)	17 (68)
Extranodal sites			
0–1	11 (85)	10 (83)	21 (84)
> 2	2 (15)	2 (17)	4 (16)
International Prognostic Index (IPI)			
0–1	4 (31)	5 (42)	9 (36)
2	4 (31)	1 (8)	5 (20)
3	4 (31)	4 (33)	8 (32)
4	1 (8)	2 (17)	3 (12)
Histology			
Follicular grade 3	1 (8)	2 (17)	3 (12)
Diffuse large B cell	9 (69)	6 (50)	15 (60)
Peripheral T cell	2 (15)	2 (17)	4 (16)
Anaplastic large-cell	1 (8)	2 (17)	3 (12)
Response at the end of therapy			
Complete response (CR) and CRu	10 (77)	5 (42)	
Partial remission	1 (8)	3 (25)	
Stable disease	0	1 (8)	
Progressive disease	0	1 (8)	
Early toxic death	1 (8)	1 (8)	
Not assessable – missing	1 (8)	1 (8)	
Confidence interval for CR rate (90%, single sided)	56–100%	22–100%	

tions of pulmonary toxicity occurred early in the treatment, after 1–3 cycles at recovery from neutropenia. None of the patients treated with CHOP developed serious pulmonary toxicity. There were no additional cases of serious pulmonary toxicity after a second course of steroids starting at day 8 was added. One patient died because of tumor lysis syndrome in the CHOP arm.

Feasibility

Fourteen percent of cycles in the (R)CHOP arm and 13% in the Gem-(R)CHOP arm were delayed. Median administered doses of cytotoxic drugs were 749 vs. 756 mg/m² for cyclophosphamide, 51 vs. 49 mg/m² for doxorubicin, and 1.2 vs. 1.1 mg/m² for vincristine. The

Table 2 Toxicity

Toxicity type and grade	Treatment	
	(R)CHOP (n = 12) n (%)	Gem-(R)CHOP (n = 12) n (%)
Neutropenia		
3	2 (17)	3 (25)
4	6 (50)	9 (75)
Thrombocytopenia		
3	0	3 (25)
4	0	4 (33)
Anemia		
3	1 (8)	6 (50)
4	0	3 (25)
Infection/febrile neutropenia		
3	2 (17)	4 (33)
4	3 (25)	1 (8)
Metabolic/laboratory		
3	1 (8)	2 (17)
Constitutional		
3	1 (8)	2 (17)
Gastrointestinal		
3	3 (25)	3 (25)
4	1 (8)	1 (8)
Hemorrhage		
3	0	3 (25)
Pulmonary		
3	0	2 (17)
4	0	1 (8)
Tumor lysis syndrome		
4	1 (8)	0

dose of gemcitabine administered on day 8 was omitted in 11% of treatment cycles. One patient in the (R)CHOP arm and two in the Gem-(R)CHOP arm failed to complete treatment because of toxicity.

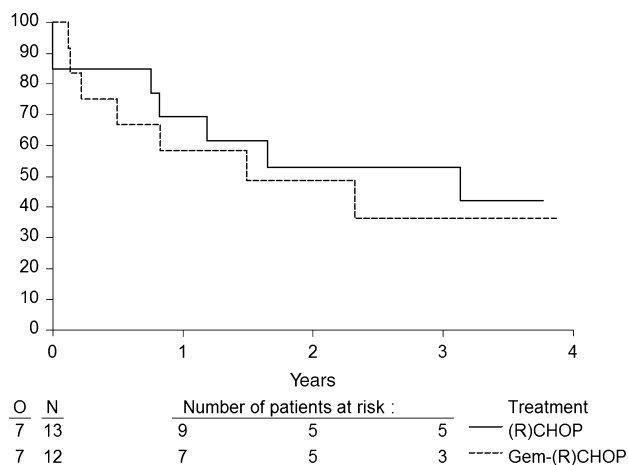
Efficacy

Ten of 13 patients achieved CR after (R)CHOP (Table 1); two of three with T-NHL, five of seven with DLBCL treated without rituximab, and three of three treated with rituximab. Five of 12 patients achieved CR after Gem-(R)CHOP; three of four with T-NHL, one of seven with DLBCL treated without rituximab, and one of one treated with rituximab.

At the time of analysis, 11 patients have not failed treatment. Median time to treatment failure was 3.1 yr (95% confidence interval 1.2-N) in the (R)CHOP and 1.5 yr (95% confidence interval 0.5-N) in the Gem-(R)CHOP arm (Fig. 1).

Discussion

The number of patients enrolled in this trial is limited because of low accrual in the second part of the study,

**Figure 1** Time to treatment failure.

caused most probably by the reluctance of physicians to randomize patients to a treatment that might result in serious pulmonary toxicity. Although the trial was therefore underpowered to determine the efficacy of the Gem-(R)CHOP regimen at the statistical levels originally planned, results do not suggest that it has significantly increased efficacy in comparison with (R)CHOP. To our knowledge, this is the second trial reporting outcomes of newly diagnosed patients with aggressive NHL treated with a gemcitabine-containing regimen. In the other, a single dose of gemcitabine 600 mg/m² on day 1 was added to CHOEP and only patients with T-NHL were included (18). Similar to our trial, results were not significantly different from controls but no pulmonary toxicity was noted. The reason for the apparently lower efficacy of Gem-(R)CHOP in our study in comparison with (R)CHOP is not completely clear. It could be caused by increased toxicity of the experimental combination. Alternatively, it might be because of chance alone; the patient numbers are small, 95% confidence intervals of response rates are wide and overlapping (Table 1), and survival curves merge.

The MTD of gemcitabine was found to be 800 mg/m² given on days 1 and 8 of each cycle. This is lower than we originally expected. The same amount of gemcitabine could be given per cycle in the ABVG and only half as much in the BAGCOPP regimen in de-novo HL (15, 16), in both cases because of hematologic toxicity. This indicates that the hematologic toxicity of gemcitabine combinations is more pronounced than that of similar etoposide-containing combination regimens (e.g., CHOEP and BEACOPP).

Pulmonary toxicity was the only prominent non-hematologic toxicity. Gemcitabine-induced pulmonary toxicity was recognized soon after the drug was introduced, but is rare in patients with solid tumors unless the drug is

combined with radiation or taxanes (19–21). Three types of lung damage are recognized: alveolar capillary leak syndrome, diffuse alveolar damage, and alveolar hemorrhage (22). The mechanisms underlying pulmonary side effects of gemcitabine have not been elucidated. Increased release of proinflammatory cytokines, TNF- α , IL-1, and IL-6, in the lungs was suggested to play a role (23). This theory is consistent with clinical observations that the lung toxicity is not dose dependent, frequently responds to steroid treatment, more pronounced in combinations with cytotoxic drugs or radiation which have a similar cytokine-release pattern and in patients with intrathoracic tumors and a prominent inflammatory component as is frequent in de-novo lymphomas. The temporal characteristics of pulmonary toxicity observed in our study also fit well into this theory. Gemcitabine is frequently used for salvage treatment of patients with lymphoma. Despite this, pulmonary toxicity was noted only in a trial where gemcitabine was given in combination with SGN-30, an anti-CD30 monoclonal antibody that presumably also causes pulmonary toxicity (24). Again, this might be explained by the fact that in the salvage setting the inflammatory response is less prominent than in newly diagnosed patients.

Because in this small group of patients, addition of gemcitabine did not seem to improve outcomes while it resulted occasionally in severe, potentially fatal, pulmonary toxicity, we conclude that further exploration of the combination of gemcitabine with (R)CHOP does not seem to be warranted.

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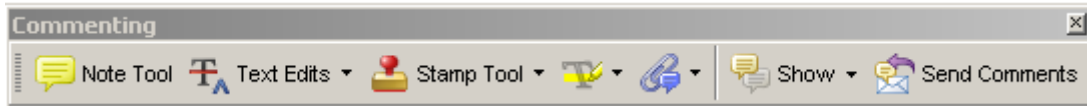
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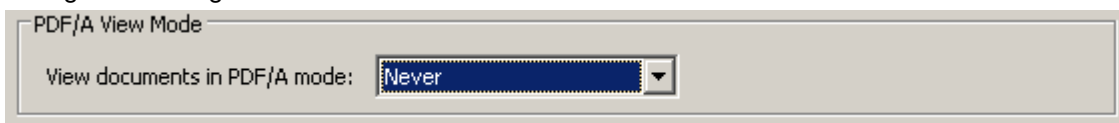
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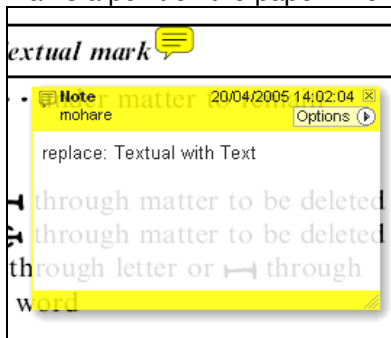
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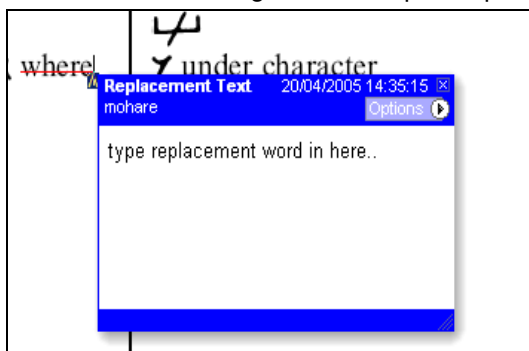


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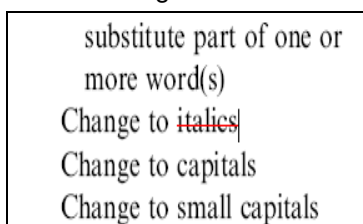


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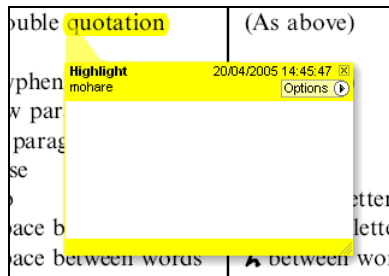


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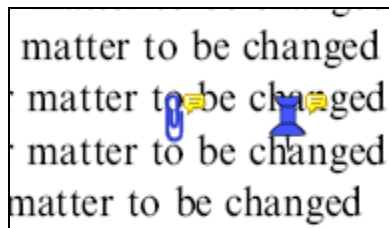


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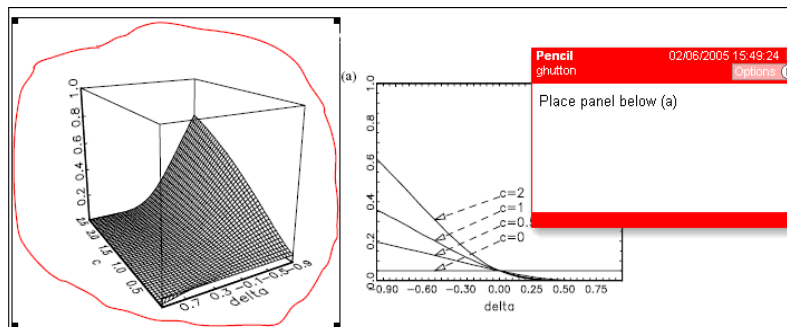


How to use it:

1. Click on paperclip icon in the commenting toolbar
2. Click where you want to insert the attachment
3. Select the saved file from your PC/network
4. Select appearance of icon (paperclip, graph, attachment or tag) and close

Pencil tool — For circling parts of figures or making freeform marks

Creates freeform shapes with a pencil tool. Particularly with graphics within the proof it may be useful to use the Drawing Markups toolbar. These tools allow you to draw circles, lines and comment on these marks.



How to use it:

1. Select Tools > Drawing Markups > Pencil Tool
2. Draw with the cursor
3. Multiple pieces of pencil annotation can be grouped together
4. Once finished, move the cursor over the shape until an arrowhead appears and right click
5. Select Open Pop-Up Note and type in a details of required change
6. Click the X in the top right hand corner of the note box to close.

Help

For further information on how to annotate proofs click on the Help button to activate a list of instructions:

