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ORIGINAL PAPER

Adding high-dose tamoxifen to CHOP does not influence response or survival in aggressive non-Hodgkin's lymphoma: an interim analysis of a randomized phase III trial

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Purpose: CHOP is the standard regimen currently used in the management of the majority of patients with aggressive non-Hodgkin's lymphoma (NHL). However, CHOP only produces 30–35% long-term survival. We hypothesized that adding high-dose tamoxifen, which is known to have multiple drug resistance-modulatory effects, to the CHOP regimen could increase the response rate, and consequently enhance the survival of patients with NHL.
Patients and Methods: In a prospective, controlled, and randomized study, eligible adult patients with aggressive NHL were randomized between CHOP only (Group I), or CHOP plus high-dose tamoxifen (Group II). The primary aim was to assess the effect of tamoxifen on complete response (CR) rate, with the secondary evaluation of tamoxifen potential impact on survival. The interim analysis of this study is presented.
Results: Fifty-one and forty-seven evaluable patients were randomized to Group I and Group II, respectively. The median age of all patients was 53 y (range 18–78 y). The two groups had comparable distributions of the pretreatment prognostic variables. The CR for patients in Group I was 80% (41 patients) as compared with 74% (35 patients) in Group II ($P = 0.48$). Likewise, there was no apparent difference in the partial remission rates between the two groups (6% *vs* 15%, respectively). Of patients who initially attained CR, 15 (37%) and 10 (29%) subsequently relapsed in Groups II and I respectively ($P = 0.45$). The NHL International Prognostic Index (IPI) was the only factor that predicted attaining CR. At the time of this interim analysis, the actuarial-estimated overall survival (OS) probability (±S.E.) for the entire population at 5 y was 58% (±6) with no survival difference between the two groups ($P = 0.51$). Only attaining CR and the IPI predicted

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OS probability. The probability of remaining event-free at 5 y (±SE) for those achieving CR was 72% (±9), and there was no significant difference between the two treatment groups ($P=0.68$). Toxicity profile was similar in the two groups.

Conclusion: Based on this interim analysis, combining high-dose tamoxifen, as used in this study, with the CHOP regimen has failed to have any favorable effect on the outcome of patients with aggressive NHL, and therefore cannot be recommended for future trials.
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Introduction

Combination chemotherapy is the mainstay of the management of most patients with advanced intermediate- and high-grade non-Hodgkin's lymphoma (NHL). First generation regimens such as CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) have produced 40–55% response rates with 30-35% long-term survival.[1] In attempts to increase the response rates and hence survival, more intense second- and third-generation regimens such as mBACOD and MACOP-B, respectively, have been used.[2,3] Nevertheless, a large prospective study that compared CHOP against the more intense regimens mBACOD, ProMace-CytaBOM, or MACOP-B found no significant difference in response or survival.[4] The latter study concluded that CHOP, which is less expensive and more tolerable, is the preferred regimen for patients with advanced aggressive NHL. Other studies have also derived the same conclusion.[5]

Primary or acquired overexpression of multidrug resistance (MDR) gene (mdr-1) leading to overproduction of the transmembrane transport protein P-gp, particularly to doxorubicin in NHL, has been linked to failure to attain a higher response rate and has been attributed to disease relapse.[6] This phenomenon is associated with reduced intra-cellular drug concentration due to decreased drug influx,[6,7] enhanced rate of efflux,[6,8] or both. Various therapeutic approaches have been pursued to overcome that type of resistance among patients with NHL.[9,10]

Tamoxifen was shown to overcome MDR-mediated doxorubicin resistance *in vitro* with an apparent dose–response relation.[11] The precise mechanism by which tamoxifen modulates MDR is not clear; however, it may not directly involve altering doxorubicin intracellular concentration.[12] Moreover, tamoxifen was shown to have other anti-tumor effects independent of its anti-estrogenic properties. The drug has a potent inhibitory effect on protein-kinase-C.[13] The latter normally transduces a variety of growth promoting signals and may have an important role in tumor growth. Tamoxifen also serves as a calmodulin inhibitor,[14] and it has the potential of reducing the level of insulin growth factor I, an autocrine growth factor.[15] Furthermore, the drug also demonstrates a stimulatory effect on the production of growth inhibitory transforming growth factor beta.[16]

Intermittent use of high-dose tamoxifen to achieve a high concentration that influences MDR has been attained without appreciable toxicity.[17] Moreover, no significant toxicity has been demonstrated in clinical studies when high-dose tamoxifen was used in combination with doxorubicin, vincristine, and etoposide,[18] or with vinblastin.[19] Furthermore, as has shown in our laboratory, the administration of tamoxifen had no unfavorable effect on the pharmacokinetics of doxorubicin when used in the CHOP regimen.[20]

To examine the potential favorable effects of adding high-dose tamoxifen to standard CHOP regimen in patients with aggressive NHL, this prospective, controlled, and randomized trial was conducted. The primary end point was to assess the influence of tamoxifen on CHOP response, while the secondary end point was to determine the effect on survival. The results of the interim analysis are presented.

Patients and methods

Study population

Between January 1994 and January 1998, consecutive eligible adult patients with NHL were enrolled. Patients were eligible if they were more than 18 and less than 80 years of age, had biopsy-confirmed NHL with pathological features of any intermediate- or high-grade

disorder other than lymphoblastic lymphoma (that is, patients in the Working Formulation groups D through H and group J),[21] had measurable disease, and had performance status of 0–3 based on the ECOG criteria.[22] All pathologic specimens were reviewed by reference hematopathologists. It was required that eligible patients have an absolute neutrophil count (ANC) $> 1.0\times10^9$/l and platelet count $> 100\times10^9$/l. Patients with abnormal hepatic and/or renal functions not believed to be attributed to lymphoma were excluded. The study was approved by King Faisal Specialist Hospital and Research Center's Research Advisory Committee, and all patients gave written informed consent.

Clinical evaluation

All patients were clinically staged with complete history and physical examination, routine laboratory studies, chest roentgenogram, computed tomography of the chest, abdomen and pelvis, bone marrow aspirate and biopsy, and percutaneous liver biopsy if it was suspected to be involved. Liver and spleen scan, bone survey and scan, gallium scan, and abdominal ultrasound were done only if indicated. Magnetic resonance imaging was also performed for some patients. Cardiac assessment including clinical examination by a cardiologist, ECG, and echocardiogram was done routinely for all elderly patients and when otherwise indicated. Any positive studies detected on staging were followed for response evaluation. Laparotomies were not routinely performed for staging or restaging; however, some patients presenting with abdominal disease had diagnostic laparotomy. Assigning the stage of the disease was according to the Ann Arbor Conference criteria.[23]

At the end of the scheduled therapy the treatment was stopped, and 1 month later each patient was restaged for evidence of residual disease. Restaging included a physical examination, laboratory and relevant radiological studies, bone marrow aspiration and biopsy, and biopsy of any previously involved extranodal sites where feasible.

Therapy

CHOP was given as a standard-dose regimen[1,4] for a minimum of 6 cycles (planned 6–8 cycles) with a three-week interval between consecutive cycles. After 2–3 courses of therapy, patients who demonstrated treatment failure (TF), as defined below, and those who only achieved partial remission (PR) were managed according to the discretion of their treating physicians using an alternative chemotherapy combination and/or radiation. For patients ≤ 60 y of age, full dose CHOP was offered if the minimal hematological entry criteria were met; however, a 25% reduction of both doxorubicin and cyclophosphamide dosages was made if the post-chemotherapy ANC nadir was $< 0.5\times10^9$/l and/or platelet count nadir was $< 50\times10^9$/l. Patients > 60 years of age were initially given 75% of the planned dose of doxorubicin and cyclophosphamide; however, if they did not demonstrate bone marrow suppression (ANC $> 1.0\times10^9$/l and platelet count $> 100\times10^9$/l at nadir), a 10% dose escalation of both doxorubicin and cyclophosphamide was used at each successive cycle until full dose was achieved. Consolidative radiation therapy was offered to those with initial bulky disease. None of the patients had CNS disease at presentation and CNS prophylaxis was not considered for patients based on specific tumor anatomical location, tumor grade, histological type, or bone marrow involvement. High-dose tamoxifen was given as two daily oral doses of 240 mg each for 5 d to be initiated on day -3 prior to each CHOP cycle.

Definition of response and survival

Complete remission (CR) was defined as the disappearance of all clinical evidence of active tumor and normalization of all laboratory and radiological abnormalities related to the disease for a minimum of 4 weeks. With the advent of modern radiographic techniques, residual abnormalities of various sizes have frequently been detected after treatment. Therefore, in this study the rate of CR was estimated conservatively; no peripheral disease could be present, and any abnormalities detected on chest or abdominal radiography had to be less than 2.5 cm in diameter with subsequent stabilization for at least 3 months after treatment. PR was indicated by a decrease of 50% or greater in the sum of the products of the maximum perpendicular diameters of each site of measured lesions, lasting at least 4 weeks. Tumor reduction of less than 50%, transient response of less than 1 month, or disease progression were considered as TF. Disease progression was indicated by the appearance of new

lesions, or by a 25% increase in the size of any preexisting lesion(s).

Overall survival (OS) was measured from the date of diagnosis to death (of any cause) or the date of the last contact. The time to treatment failure (TTF) was measured from the date of diagnosis to disease progression, relapse, or death only for those attaining CR.

Study design, data analysis, and statistical methods

A prospective, stratified, randomized, and controlled design was used. Eligible patients were first stratified according to age, performance status, and stage and were then randomized to either CHOP only (Group I) or CHOP plus high-dose tamoxifen (Group II). Randomization was done by a research coordinator using a computer-generated random table.

Sample size was determined based on the assumption that the addition of tamoxifen could increase the CR rate by 15%. Furthermore, we considered the proportion of patients who would survive at least for two years from entry without relapse. From available literature, around 50% of patients remained disease-free for two years. This proportion was postulated to increase by 15–20% by the addition of tamoxifen. Using the procedure proposed by Freeman,[24] it was estimated that approximately 90 patients needed to be assigned to each group to reach a statistical power of 80% (type II error of 20%) with a type I error equal to 0.05. An interim analysis was planned when 50% of the needed sample for each arm was accrued. For the interim analysis a two-sided P-value ≤ 0.01 was considered significant.

A computerized database was assembled to include patients' characteristics, and all relevant clinical, laboratory, and radiological data. Also included were therapy details, response and follow-up. No patient was excluded from the analysis because of major protocol violation, recent entry, insufficient data, incomplete therapy, toxicity, or early death. The two treatment groups were compared for the prevalence of the pretreatment baseline patients and disease variables using X^2, X^2 with Yates' correction, or Fisher's exact test where appropriate. Various prognostic factors, including the potential effect of tamoxifen, were tested for their unadjusted association with CR in a univariate analysis. Variables with a P-value of ≤ 0.10 were included in a stepwise multivariate regression analysis to identify the independent predictors for response.[25] Age was entered both as continuous and as dichotomous values by using different cutoffs. OS and TTF were estimated according to the Kaplan–Meier method.[26] The difference in survival between groups was compared by the log-rank test of Mantel–Cox.[27] The odd ratios of fixed covariates that have independent influence on survival were measured using the proportional hazards model of Cox.[28] All tests of significance were two-sided. Data analysis was carried out using programs from the BMDP Statistical Software.[29]

Results

Fifty-one eligible patients were randomized to Group I, and forty-nine to Group II. Of the latter group, 2 patients refused tamoxifen and therefore excluded from further analysis. The current interim analysis addresses the outcome of 98 evaluable patients (51 in Group I, and 47 in Group II). The median age of all patients was 53 y (range 18–78 y) with no difference in the median age of those patients randomized to Group I (51 y) and those in Group II (52 y) ($P = 0.96$). Table 1 depicts the lack of significant differences in the distribution of any of the known pretreatment prognostic variables between the two treatment groups. Moreover, the two groups had similar prevalence of other variables such as bulky *vs* non-bulky disease, sites of extranodal involvement, and pathologic grades.

Analysis of response

Table 2 shows that in Group I, 80% of patients attained CR (95% CI, 69–91%) as compared with 74% (95% CI, 61–87%) for patients randomized to Group II ($P = 0.48$). There was no difference in the median number of courses given of CHOP (5 courses each), and there was no inequality in dose intensity in the two groups (data not shown) to account for the lack of difference in the CR rate. Consolidative radiotherapy was given to 10 and 8 patients in Groups I and II, respectively.

Of the 41 patients who initially attained CR in Group I, 15 (37%) subsequently relapsed as compared with a relapse rate of 29% among patients randomized to Group II (10 patients out of 35). That difference was

Table 1 Pretreatment patients' and disease's characteristics

	CHOP no. (%)	*CHOP + tamoxifen no. (%)*	*P-value*
Total numbers	51 patients	47 patients	
Age			0.54
≤ 50 y	34 (67)	34 (72)	
> 50 y	17 (33)	13 (28)	
Sex			0.60
Males	32 (63)	30 (63)	
Females	19 (37	17 (37)	
B symptoms			0.74
No	32 (63)	28 (60)	
Yes	19 (37)	19 (40)	
Performance status*			0.47
0	3 (6)	7 (15)	
1	37 (72)	30 (64)	
2	9 (18)	9 (19)	
3	2 (4)	1 (2)	
Stage†			0.75
I	7 (14)	5 (11)	
II	18 (35)	19 (40)	
III	11 (22)	6 (13)	
IV	15 (29)	17 (36)	
Extranodal involvement			0.35
No	41 (80)	34 (72)	
Yes	10 (20)	13 (28)	
Lactic dehydrogenase			0.35
Normal	17 (33)	14 (30)	
Abnormal	34 (67)	33 (70)	
IPI (risk)‡			0.98
Low	9 (18)	7 (15)	
Low-intermediate	13 (25)	12 (25)	
Intermediate-high	21 (41)	20 (43)	
High	8 (16)	8 (17)	

*Performance status based on the ECOG criteris [22].
† Stage based on the Ann Arbor Conference criteria [23].
‡ IPI denotes International Prognostic Index [30].

Table 2 Response rates attained in the two treatment groups

Response	*CHOP no. (%)*	*CHOP + tamoxifen no. (%)*
Complete remission	41 (80)	35 (74)
Partial remission	3 (6)	7 (15)
Treatment failure	7 (14)	5 (11)

not statistically significant ($P = 0.45$). There was no apparent difference in the relapse patterns in the two groups.

Of various factors found to be associated with the likelihood of attaining CR with a P-value ≤ 0.1 on the unadjusted analysis (Group I *vs* Group II not included), only the International Prognostic Index (IPI)[30] remained independently significant in the multiple regression model. The odds ratio (± s.e.) of achieving CR for patients in the high-risk IPI category was only 0.26 (± 0.09) as compared with those in the low-risk group.

Analysis of survival

Over a median follow-up of 39 months (range 24 – 57 months), 54 patients (55%) were alive and disease-free, while 8 (8%) were alive with evidence of disease. The remaining 36 patients (37%) were dead from disease, or from disease- and/or therapy-related complications. In Group I, 26 (51%), 4 (8%), and 21 (41%) of patients were alive and disease-free, alive with evidence of disease, and dead, respectively. The corresponding figures for Group II were 28 (60%), 4 (8%), and 15 (32%), respectively. That difference was not statistically significant ($P = 0.63$).

The median OS for the entire population has not been reached; however, the actuarial-estimated survival probability at 5 y (± s.e.) was 58% (± 6). Comparing the OS in Groups I and II (Figure 1) failed to show any statistically significant difference ($P = 0.51$); however, the median survival was not reached for either group.

The proportional hazards model of Cox identified the IPI as the sole variable that independently influenced survival. The odds ratio (± s.e.) of death for patients in the high-risk group was 4.44 (± 1.71) as compared with those in the standard low-risk group. On the other hand, when attaining CR was included as an

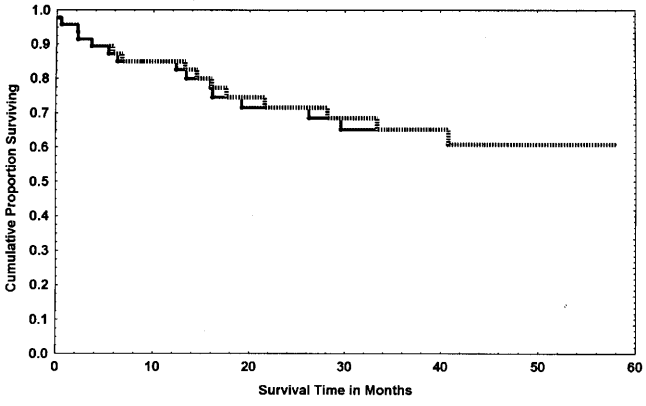

Figure 1 *The overall survival curves of Group I (solid line) and Group II (dashed line).*

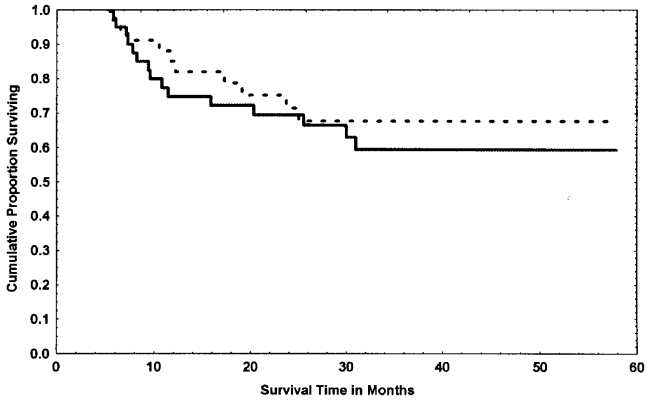

Figure 2 *Time to treatment failure curves for Group I (solid line) and Group II (dashed line).*

explanatory variable it produced the highest predictive value, where those who failed to achieve CR had an odds ratio (±s.e.) of death of 13.6 (±1.43) as compared with those who demonstrated CR. In the latter model, the independent influence of IPI persisted.

Analysis of TTF of those 76 patients who achieved CR was also carried out. Again the median TTF has not been reached; however, the probability of remaining event-free at 5 y (±s.e.) was 72% (±9). Analysis of TTF based on treatment groups was also done. Figure 2 depicts the lack of significant difference in the TTF between the two treatment groups ($P = 0.68$).

Despite increasing number of iterations, and relaxing entry and removal criteria, the proportional hazards model of Cox did not identify any independent variable that appears to influence TTF.

Toxicity

Table 3 shows the comparisons of demonstrated grade III toxicity in Groups I and II. The table indicates that there was no evident difference between the two groups. None of the patients developed cardiomyopathy, hemorrhagic cystitis, thromboembolic episodes, ataxia, or toxic death.

Table 3 Grade III toxicity in the treatment groups

Toxicity	*CHOP no. (%)*	*CHOP + tamoxifen no. (%)*
Alopecia	23 (45)	20 (43)
Mucositis	8 (16)	6 (12)
Nausea and/or vomiting	1 (2)	1 (2)
Diarrhea	0 (0)	1 (1)
Anorexia	0 (0)	1 (1)
Neuropathy	2 (4)	1 (1)
Febrile neutropenia	4 (8)	6 (12)
Anemia	3 (6)	0 (0)

Discussion

Combination chemotherapy remains the treatment of choice for most patients with aggressive NHL. The outcome of patients using the more intense second- or third-generation combination chemotherapy was not found superior to that attained with standard CHOP.[1,4,5]

Tamoxifen has been shown to possess several antitumor properties that are not related to its known antiestrogenic effect.[13–16] It was also shown that the drug could overcome MDR-mediated doxorubicin resistance.[11,17] The latter, has been attributed to some of the treatment failure among patients with NHL.[6–10] Nonetheless, in this study, adding high-dose tamoxifen to standard CHOP regimen in patients with aggressive NHL was not found to be beneficial.

80% of patients randomized to Group I (CHOP) attained CR (95% CI, 69–91%) as compared with 74% (95% CI, 61–87%) for patients randomized to Group II (CHOP + tamoxifen) ($P = 0.48$). It is notable that the attained CR in both groups were higher than that of 44% recently reported by Fisher *et al*.[4] Furthermore, subsequent relapse was also similar in the two groups (37% in Group I *vs* 29% in Group II) ($P = 0.45$). Only patients' risk stratification according to the IPI, predicted the likelihood of achieving CR, while adding tamoxifen to CHOP was not an independent predictor of response.

At final analysis, 51%, 8%, and 41% of patients in Group I were alive and disease-free, alive with evidence of disease, and dead, respectively. The corresponding rates for Group II were 60%, 8%, and 32%, respectively ($P = 0.63$). The 5-y OS probability for the entire group was 58% (±6), with no OS difference between Groups I and II ($P = 0.51$). Attaining CR and membership of the IPI risk strata were the only variables that independently influenced OS. Likewise, analysis of TTF failed to demonstrate a significant difference between the two groups ($P = 0.68$), with an overall 5-y TTF probability for the entire population equal to 72% (±9).

As shown in earlier studies,[17–19] the addition of high-dose tamoxifen in the dosage used in the current

trial did not enhance the toxicity of CHOP. It is conceivable that the lack of effect on the doxorubicin pharmacokinetics may account for the absence of increase in doxorubicin toxicity.[20]

One plausible argument that may explain the absence of an effect for high-dose tamoxifen is that all patients in this series were previously untreated, and hence, the overexpression of mdr-1 may have not been high enough to allow tamoxifen to demonstrate any advantage. On the other hand, while overexpression of mdr-1 MDR gene among previously treated patients have been reported to range from 50% to 65%, the rate in untreated patients ranges from 20% to as high as 50%.[6,31] Therefore, it appears unlikely that the overexpression rate of mdr-1 alone can account for the lack of benefit. However, a different outcome may have obtained if tamoxifen was used as a modulator for patients in relapse.

Another argument may be associated with the dose and/or schedule of tamoxifen used in this study and its culpability in the lack of advantageous effects. The strategy used in this trial was similar to that which was successfully used in a phase-1 study by Trump *et al* to overcome vinblastin resistance.[19] Moreover, the dosage used in the current study was identical to that used by Millward *et al* to modulate resistance against etoposide.[32] Nevertheless, as reported recently from our pharmacokinetics laboratory on randomly selected comparable samples of 10 patients each from Group I and Group II, the tamoxifen used dose and schedule did not influence the pharmacokinetics of doxorubicin.[20]

Based on the results of the interim analysis and the arguments raised earlier, it was judicious that the trial was terminated. The appropriateness of that verdict was further reinforced by pertinacious statistical considerations. The rational for the timing of this interim analysis was alluded to in the methodology section. It is ethical to include only the minimum number of patients necessary to demonstrate a real difference in the effectiveness of treatments in order that subsequent patients can be given the superior treatment. Moreover, only one interim analysis was planned to avoid exaggerating the true *P* value for repeated analysis of accumulating data 'optional stopping phenomenon'.[33] Based on the elegant criteria illustrated by McPherson,[34] it is inconceivable that a true difference was overlooked and that the alternate hypothesis was rejected inopportunely.

We conclude that the addition of high-dose tamoxifen to standard CHOP therapy — as used in this study — had no favorable effects on the response rates or the survival of patients with aggressive NHL. To improve the currently achievable long-term outcome of those patients, novel approaches to modulate resistance using potential effective dosage and schedule are pressingly needed. Clinical investigators may need to devise imaginative new protocols combining those newer resistance modulation strategies with the intriguing concept of high-dose chemotherapy and stem cell support.[35–37] That approach may alter the practice of how we manage patients with high-risk NHL.

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