Ga-67 Uptake: a Predictor of Post-Therapy Active Residual Disease and Clinical Outcome in Patients with Diffuse Large Cell Lymphoma

Ga–67 Tutulumu: Diffüz Büyük Hücreli Lenfoma Hastalarında Tedavi Sonrası Aktif Rezidüel Hastalık ve Klinik Sonucun Belirleyicisi

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Abstract

Purpose: Diagnosis and treatment of post-therapy active residual disease (PTARD) is essential in patients with lymphoma. After treatment, Ga-67 scan is considered as a useful technique for monitoring response in these patients.

Material and Methods: Between December 1998 and January 2004, 63 patients histopathologically diagnosed with Diffuse Large Cell Lymphoma (DLCL) were studied. Patients were evaluated before and after treatment with a whole body Ga-67 scan in addition to other imaging techniques. International Prognostic Index (IPI), and clinical variables were determined according to criteria reported by the International non-Hodgkin's Lymphoma Prognostic factors Project.

Results: Among the patients with positive computed tomography (CT) scan, the 5-year relapse-free and overall survival rates were 70% and 78% for those with negative scans compared with 23% and 35% for gallium-positive patients, respectively ($p< 0.004$, $p<0.008$). Furthermore, the 5-year relapse-free and overall survival rates were 92% and %91 for those with negative scans compared with 33% and 40% for gallium-positive patients ($p< 0.001$, $p< 0.004$), among the patients with negative CT scan. All patients were divided into two groups according to the IPI index after therapy and the 5-year relapse-free survival rate for negative Ga-67 scan is 75%, as compared with 42% for restaging positive Ga-67 scan ($p<0.004$) in the patients with low IPI score.

Conclusion: Ga-67 scan is capable of detecting PTARD that remains undetected at CT and it appears to be a better predictor of outcome than previously evaluated pretreatment risk factors in patients with DLCL.

Keywords: **Lymphoma, Large B-Cell, Diffuse; Gallium citrate; Neoplasm, Residual.**

Özet

Giriş: Lenfomalı hastalarda şifa sağlamak için, tedavi sonrası aktif rezidüel hastalığın (PTARD) tanınması ve tedavi edilmesi gereklidir. Bu amaçla bu grup hastalarda, tedavi sonrası yanıtın değerlendirilmesinde Ga–67 ile tüm vücut tarama oldukça yararlı bir teknikdir.

Gereç ve Yöntem: Çalışmaya Kasım 98 ve Ocak 2004 arasında histopatolojik olarak Diffüz Büyük Hücreli Lenfoma (DLCL) tanısı alan 63 hasta alındı. Hastalar tedavi öncesi ve sonrası diğer görüntüleme yöntemlerinin yanısıra tüm vücut Ga–67 sintigrafisi ile değerlendirildi. Uluslararası Prognoz İndeksi (IPI) değişkenleri Uluslararası Non-Hodgkin Lenfoma Prognostik Faktor Projesinin önerileri doğrultusunda detaylı olarak hesaplandı.

Bulgular: CT (+) bulunan hastalar arasında, Ga–67 (-) hastaların 5 yıllık hastalıksız ve toplam sağkalımları %70 ve %78 iken Ga–67 (+) hastalarda bu oran sırasıyla %23 ve %35 idi ($P< 0.004$, $p<0.008$). Ek olarak CT (-) hastalar arasında Ga–67 (-) hastaların hastalıksız ve toplam sağkalımları %92 ve %91 iken Ga–67 (+) hastalarda bu oran %33 ile %40 olarak saptandı ($p<0.001$, $p<0,04$). Aynı şekilde tüm hastalar tedavi sonrası IPI indeksine göre iki gruba ayrıldığında düşük IPI skorlu hastalar arasında negatif Ga–67 taraması olanlarda hastalıksız yaşam süresi %75 olarak saptanır iken, bu oran pozitif Ga–67 taramasıyla yeniden evrelenen hastalarda %42 olarak kaydedilmiştir.

Sonuç: Ga–67 taraması CT ile saptanamayan PTARD sonuçlarını saptamak için uygun bir yöntemdir. Ayrıca DBBH'li hastalarda tedavi öncesi belirlenen risk faktörlerine göre daha iyi bir klinik sonuç belirleyicisidir.

Anahtar Kelimeler: **Diffüz büyük hücreli lenfoma; Ga–67 sintigrafisi; Tedavi sonrası aktif rezidüel hastalık.**

Introduction

Most patients with diffuse large cell lymphoma (DLCL) can achieve complete remission after combined chemotherapy. However, mortality is still high because of early recurrence or primary resistant disease (1, 2). Diagnosis of post-therapy active residual disease (PTARD) of lymphoma is essential for successful treatment. Estimation of outcome during early treatment may lead to a change in previous therapy, and results in a potential improvement of survival (3).

Evaluation of PTARD presence or absence during and/or after treatment still represents a complex diagnostic problem. Although conventional computed tomography (CT) scans most often reveal post-therapy residual abnormalities and provide much information regarding size and distribution of lesions, they do not always adequately distinguish active disease from benign changes such as fibrosis, necrosis or inflammation (4). Correct evaluation of PTARD existence is highly important, since adequate treatment can often lead to cure or have a significiant impact on the clinical outcome (5).

Ga-67 scan is considered as a useful technique for monitoring response after treatment of lymphoma. Kaplan et. al. have confirmed that patients with DLCL have increased Ga-67 avidity within active tumor sites (6). Moreover, Ga-67 scan has been proposed as an additional examination regarding the nature (fibrosis/necrosis vs. residual disease) and activity of these masses (7).

In present study, we prospectively assessed the ability of Ga-67 scan to define PTARD. Additionally, we evaluated whether positive post-therapy scan has an ability to predict the clinical outcome in patients with DLCL.

Patients and Methods

Between December 1998 and January 2004, sixty-three newly diagnosed consecutive patients who were histopathologically diagnosed as DLCL at Erciyes University, Dedeman Hematology Oncology Hospital were enrolled into the study. Criteria for entry into the study included: no prior therapy; histologic DLCL according to the World Health Organisation classification; an Eastern Cooperative Oncology Group performance status score of <3; and normal hepatic, renal, and cardiac function. The study was approved by Erciyes University Medical Faculty ethics committee, and informed consent was obtained from each patients.

All patients were evaluated before the treatment with a complete history and physical examination, complete blood count, chemistry profile, bone marrow trephine biopsy, CT of the chest and abdomen, and whole body Ga-67 scan. The Ann Arbor system was used for staging. Bulky lesions were defined as any pathological mass with a major diameter ≥10 cm.

The general characteristics of the patients were shown in Table I. Sixty-three patients with DLCL (37 males, 40 females; median age 52 years, range 19-71 years) were treated with standard chemotherapy regimen consisting of cyclophosphamide, adriamycin, vincristine and prednisolone (CHOP). Radiotherapy was also applied to 17 patients who had bulky tumors after the end of chemotherapy. Patients were monitored for a median of 44 months (range, 8-60 months) and restaged with Ga-67 scan other imaging methods after the whole cycles of chemotherapy or chemo-radiotherapy.

Imaging. CT scan of the chest, abdomen, and pelvis were obtained using a helical CT apparatus (Shimadzu AX-100S, Japan) with 10 mm slice thickness. Images were obtained after intravenous administration of 120-150 ml of non-ionic contrast material containing 300 mg/ml of iodine.

Ga-67 scanning was performed according to standard procedure. Patients received IV 8mCi Ga-67-citrate (Mallinckrodt, Holland). Whole body and planar images were obtained 48 and 72 h after injection; delayed views up to five days were obtained when necessary in order to make a conclusive diagnosis. Bowel cleansing was performed. Single-photon emission computed tomography (SPECT) imaging was carried out only in selected patients for making better localization.

A dual headed gamma camera (Siemens E-Cam, USA) was used. Anterior and posterior planar images were acquired for 500.000 counts with the patient supine. SPECT imaging was generally performed at 72 h after injection or later. Data were obtained in 64x64 pixel matrices through 360^{o} rotation at 6^{o} intervals, for 30 s per arc interval. Reconstruction was performed by filtered back-projection by using a Butterworth filter (cut-of frequency 0.25, power factor 8). Slice thickness was two pixels (12.8 mm) and no attenuation correction was used.

Abnormal Ga-67 uptake was defined as any focal area of increased activity outside the normal physiological

radionuclide concentration sites. The results of Ga-67 scan were evaluated by two physicians who were blinded to outcome data, pathology and CT results. The final diagnosis was made by consensus when readings were different.

Evaluation of response. Complete remission was defined as being a complete regression of all assessable disease. Partial response was defined as >50% reduction of the size of clinically apparent disease without any evidence of re-growth on completion of induction therapy. All patients had a positive Ga-67 scan at the time of diagnosis and at least one documented Ga-67 scan after the completion of combination therapy.

International Prognostic Index (IPI). clinical variables of IPI determined as detailed by the International non-Hodgkin's Lymphoma Prognostic factors Project were: age (<60 vs ≥60 years), ECOG performance status (0 or one vs 2 or more), Ann Arbor stage (I or II vs III and IV), extranodal involvement (<2 sites vs ≥2) and serum LDH levels (normal vs high) [3].

Statistical Analysis. The overall and relapse-free survival curves were calculated using the Kaplan-Maier method. The statistical significance of differences observed was assessed using the log-rank test.

Result

Evaluation of response and clinical outcome. The patients were divided into 4 groups according to the positive or negative Ga-67 scan and CT after 4-6 cycles of chemotherapy (Table II). CT scan was positive in 34 of the 63 (54%) patients. Of these, 17 of the 34 (50%) patients were Ga-67 [+] at the end of the therapy, and 13 of the 17 (76%) patients relapsed and 4 showed no evidence of disease at a median of 35 months (range, 8-60 months) from presentation. Additionally, 17 of the 34 patients, who had positive CT scans, but negative Ga-67 scan, only 5 of the 17 (29%) patients relapsed and 12 have no evidence of disease at a median of 45 months (range, 23-60 months) from initiation of the study (Table II). The 5-year relapse-free and overall survival rates were 70% and 78% for those with negative scans compared with 23% and 35% for gallium-positive patients, respectively ($p< 0.004$, $p<0.008$) (Figure 1 and 2).

At the same time, 29 of the 63 (46%) patients had negative CT scan. Of these, 15 had a positive Ga-67 scan, 10 of whom (66%) relapsed and 5 (34%) have no evidence of disease at a median of 40 months (range, 13-60 months). Of the remaining 14 of the 29 had negative Ga-67 scan of whom 2 (14%) relapsed and 12 (86%) showed no evidence of disease at a median of 48 months (range, 25-60 months) from presentation (Table II). The 5-year relapse-free and overall survival rates were 92% and %91 for those with negative scans compared with 33% and 40% for gallium-positive patients ($p< 0.001$, $p< 0.004$) (Figure 3 and 4).

International Prognostic Index (IPI). At the same time, the patients were divided into 2 groups after therapy, according to the IPI index. 48 of the 63 patients had low-intermediate IPI scores and 15 had high IPI scores. Of the 15 patients with high IPI scores, 13 had positive Ga-67 scan and all 15 patients relapsed within 30 months. Of the remaining 2 patients who had negative Ga-67 scan, one patient relapsed at 26 months and the other patient is currently in CR at 32 months after diagnosis.

Of the 48 patients with low-intermediate IPI scores, 19 had positive Ga-67 scan and the other 29 patients had negative Ga-67 scan, at the end of the therapy. At a median follow-up of 40 months, 11 patients relapsed among the 19 Ga-67 patients. By contrast, we observed only 7 relapses among the 48 Ga-67 [-] patients at a median follow-up 52 months. The 5-year relapse-free survival rate for Ga-67 [-] scan was 75%, as compared with 42% for restaging Ga-67 [+] patients ($p<0.004$) (Figure 5).

Tablo I. General characteristics of the patients

Parameters	No of patients
Total	63
Sex	
Male	37
Female	26
Stage	
I	22
II	12
III	17
IV	12
IPI score	
Low-intermediate	50
High	13
Treatment	
Chemotherapy (CHOP)	46
Chemotherapy+radiotherapy	17

Tablo II. 67 Ga findings in DLCL patients: Relationship to response and clinical outcome

		Clinical Outcome (5 year) Relapse		
Post-therapy Scan Results	n	Died	Active Tumor	NED
CT [+] / Ga-67 [+]	17	11	1	4
CT [+] / Ga-67 [-]	17	3	2	12
CT [-] / Ga-67 [+]	15	7	3	5
CT [-] / Ga-67 [-]	14	1	1	12

NED: No-evidence disease

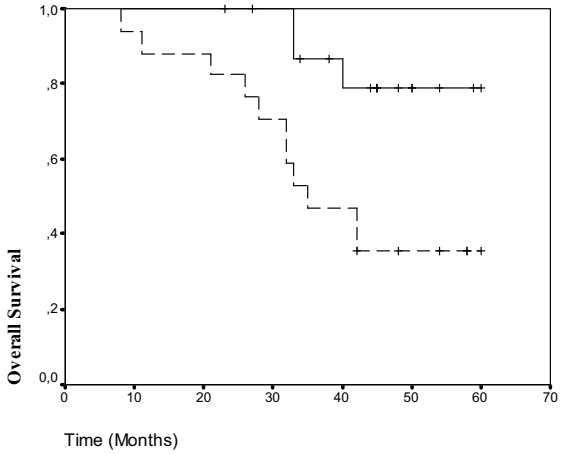

Figure 1. Overall survival curves of 34 patients with positive CT scan according to gallium scan results (Ga-67 [+] scan, 17 patients; Ga-67 [+] scan, 17 patients).

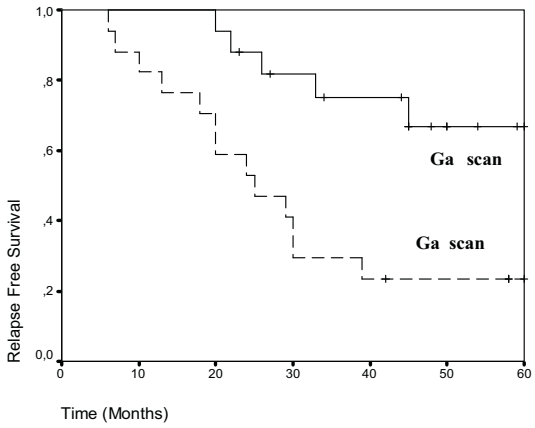

Figure 2. Relapse-free survival curves of 34 patients with positive CT scan according to gallium scan results (Ga-67 [+] scan, 17 patients; Ga-67 [-] scan, 17 patients).

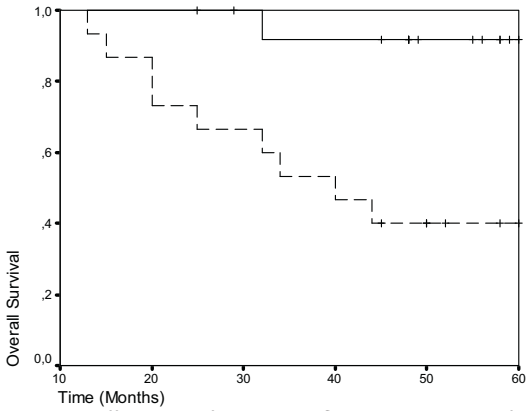

Figure 3. Overall survival curves of 29 patients with negative CT scan according to gallium scan results (Ga-67 [+] scan, 15 patients; Ga-67 [-] scan, 14 patients).

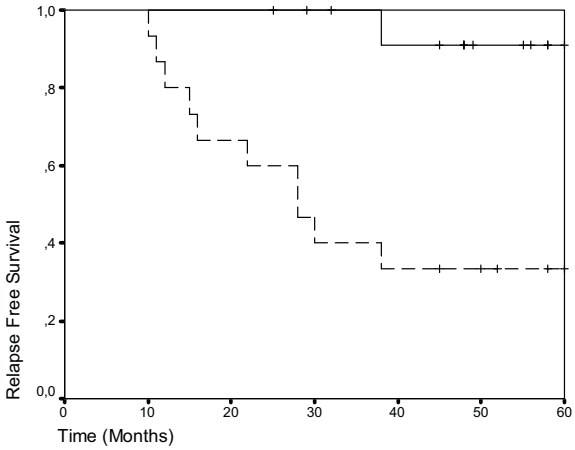

Figure 4. Relapse-free survival curves of 29 patients with negative CT scan according to gallium scan results (Ga-67 [+] scan, 15 patients; Ga-67 [-] scan, 14 patients).

Tablo III. The relationship between pretreatment IPI index and post-treatment Ga-67 uptake in 63 DLCL patients

Post-treatment	Pretreatment IPI	
SCAN	Low-Intermediate risk	High risk
Ga-67 [+] (n=32)	19	13
Ga-67 [-] (n=31)	29	2
TOTAL	48	15

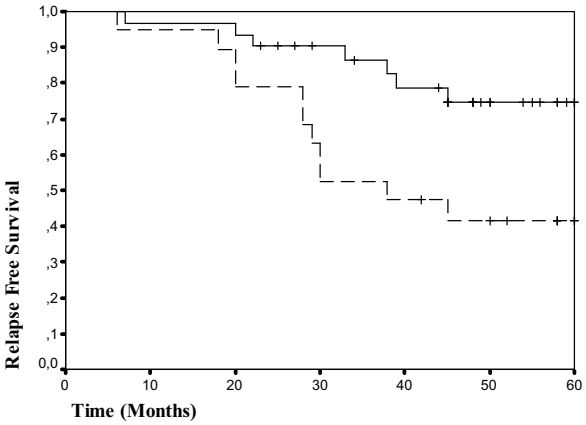

Figure 5. Relapse-free survival curves of 48 patients with low-intermediate IPI score according to gallium scan results (Ga-67 [+] scan, 19 patients; Ga-67 [-] scan, 29 patients).

Discussion

Few clinical tools are available to help identify patients in apparent CR or PR who have occult residual disease. Incomplete regression of lymphamatous mass despite apperently effective therapy constitutes a major problem in the treatment of lymphoma. In many cases, such residual masses consist of residual fibrotic tissue with no active lynphamatous component, while in other cases active residual disease may still be present. This dilemma may occur after combined modality treatment in both DLCL patients with or without mediastinal involvement. There are several reports related with Ga-67 scan for discriminating between active residual tumour and benign fibrous tissue [8-11]. The present study on a large number of diffuse large cell lymphoma patients provides definitive confirmation of utility of Ga-67 scan as a specific tool for discriminating fibrotic and tumor tissue and therefore its validity in the follow-up of mediastinal masses in these lymphomas.

Clinical pretreatment risk factors evaluated in patients with DLCL show tumor characteristics and the effect of lymphoma on patients. In the population sample of 2031 patients analyzed by the International group project most of the clinical risk factors were significant in the univariate analysis [3]. Janicek et al [12] showed that Ga-67 differentiated the patients with a good and with a poor prognosis, even when risk factors predicted poor outcome. According to our findings, Ga-67 scan in 63 patients after 4-6 cycles was a good predictor of outcome in patients with DLCL. There was a significant difference in response rate, 5-year RFS and OS between patients with positive and negative Ga-67. Furthermore, our results suggested that the patients with positive Ga-67 scan performed at the end of treatment had significantly shorter RFS compared with negative scan among the patients with low IPI score before treatment.

In conclusion, Ga-67 scan is valuable for discriminating between residual tumor and fibrosis/necrosis in DLCL patients who had positive CT scan after chemotherapy and it may be capable of detecting PTARD that remains undetected at CT. At the same time, Ga-67 may be used as a predictor of outcome as well as pretreatment risk factors such as IPI score applied in patients with DLCL. On the other hand, positive emission tomography (PET) scan detects more disease sites both above and below the diaphragm on staging of lymphoma than gallium. Therefore, in recent years, it has been rapidly replaced Ga-67 imaging in the staging and follow-up of patients with lymphoma. However, Ga-67 appears to be still an effective predictor of post-therapy active residual disease especially in developing countries such as Turkey that can not routinely use the PET scan because of financial problems.

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