

Ga-67 scintigraphy in lymphoma patients undergoing bone marrow transplantation

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ABSTRACT

It is aimed to evaluate Gallium-67 scintigraphy (GS) and CT for predicting clinical outcome in lymphoma patients who undergo autologous stem-cell transplantation (ASCT). Forty patients undergoing ASCT, had GS before and at 100 days post-transplantation (D-100). Patients were followed for 6-61 months and 15 had repeat GS at 200 days post-transplantation (D-200). All patients underwent computed tomography (CT) imaging. Out of 40 patients, 15 were diagnosed with Hodgkin's Disease and 25 with non-Hodgkin lymphoma. Fifteen had pathologic D-100 GS, where 7 were correlated with CT. Out of 8 patients with normal CT, 6 had control studies. Two patients returned to normal, 1 showed persistence and 3 were accepted in relapse due to progressive lesions on GS with new appeared lesions on CT. Four patients with pathologic findings on D-100 CT but normal GS, were in remission on follow-up. Of the patients 85.7% with negative and 28% with positive D-100 GS were disease-free (median follow-up: 30 months). The PPV, NPV and accuracy for GS were 64%, 88% and 77.5%, respectively, and 37.5%, 75% and 75% for CT, suggesting importance of D-100 GS in the prediction of outcome in lymphoma patients who undergo ASCT. GS is superior compared to CT for the prediction of progression. [Turk J Cancer 2007;37(2):54-58]

KEY WORDS:

Lymphoma, Gallium-67 scintigraphy, autologous stem-cell transplantation, prognostic value

INTRODUCTION

The success rate of combination chemotherapy is very high in patients with Hodgkin's disease (HD) and non-Hodgkin lymphoma (NHL). However, 10-20% of patients with HD and 30 to 60% of patients with NHL relapse eventually (1-7). A subgroup of patients, in which standard chemotherapy fails, requires salvage cytoreductive chemotherapy followed by high-dose chemotherapy supported by autologous stem-cell transplantation (ASCT). This procedure often offers the final chance of long-term survival (1-7). The success rate of ASCT depends on age, concurrent medical conditions, the Karnofsky global performance status, the histologic type of lymphoma and the number of extranodal disease sites (8,9). However, the most important factor influencing the success rate of ASCT is the tumor response to salvage chemotherapy (6,7,10). Currently, this response and further prognostic information following ASCT is evaluated by Gallium-67 scintigraphy (GS) and computed tomography (CT).

The use of Gallium-67 scintigraphy (GS) in the management of patients with HD and NHL has been evaluated significantly in very large series (11). GS provides metabolic image of tumor burden relying on the differential uptake of Gallium-67 (Ga-67) between normal and malignant tissue. Comparisons between GS and computed tomography (CT) in the evaluation of lymphoma patients suggest that GS has a superior predictive value for relapse, besides the prognostic value of GS in assessing residual mass in between and at the end of therapy is well documented (11). However, little is

known about its role in ASCT. The purpose of this study is to evaluate the predictive value of GS and compare this with CT in patients with chemosensitive relapse who underwent high dose chemotherapy and ASCT.

MATERIALS AND METHODS

The database of allografts for HD and NHL performed in our institution between May 2000 and August 2005 was cross-referenced with the nuclear medicine patient database to identify cases in which GS had been used at least once before and post-transplantation. A total of 40 patients were studied. Patients were followed-up for a median of 29 months (range: 6-61 months).

GS was performed 48 hours after an intravenous injection of 300 MBq (8 mCi) Ga-67. In some patients 72-hour imaging was performed due to delayed bowel excretion. Whole body anterior and posterior planar images were obtained as well as neck, thorax, abdominal and pelvic SPECT images with a medium energy, general purpose collimator mounted on gamma camera (ADAC and Siemens). All patients had at least one GS prior ASCT to show that their disease is gallium avid. GS was performed 100 days after ASCT as their first scintigraphic control and 16 patients had another follow-up scintigraphy on D-200 and 1 patient underwent PET scintigraphy. Written reports of the gallium studies were obtained from the archive, which have been read by nuclear medicine physicians. An abnormal Ga-67 tumor uptake was defined if any focal or diffuse area of increased activity in a location that is incompatible with normal anatomy. In the follow-up studies special attention was directed to the sites of previously defined disease.

All patients had consecutive CT studies of their disease related areas -chest, abdomen and pelvis- at the same time intervals of GS. Written reports were taken into consideration primarily to establish the predictive value of CT imaging. CT scans were accepted abnormal if a lymph node ≥ 1 cm was present or any mass that was incompatible with normal anatomy.

Statistical Analysis

Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy were calculated by standard methods.

RESULTS

The total number of patients enrolled in this study was 40, of whom 15 were diagnosed with HD and 25 with NHL. All patients underwent ASCT. The study population composed of 14 female and 26 male patients with an age range of 16 to 61 (median: 41 years). Median follow up was 29 months (range: 6-61 months). All patients had at least one baseline gallium scan on the course of their disease treatment which proved that their disease was gallium avid.

Fifteen patients showed pathologic radiogallium distribution on D-100 which corresponded to 7 patients out of 16 with pathologic CT findings (Table 1). Out of 8 patients without any corresponding disease on CT (Figure 1), 6 had follow-up studies on D-200. On these, out of 3 patients with hilar uptake on D-100 scan, 2 of them returned to normal while 1 patient with asymmetrical hilar Ga-67 uptake, showed persistence. The other 3 patients developed progressive disease and this time not only GS but also CT scans were positive.

On the other hand, 4 patients with pathologic sites on CT, but normal radiogallium distribution on D-100 (Figure 2), revealed normal findings on clinical follow-up and D-200 CT imaging as well as GS.

On the clinical follow-up, 3 patients had relapsed disease at 11, 12 and 13 months post-ASCT and were put on salvage treatments. Two of those had true-positive GS and the one with isolated CNS relapse had a false-negative D-100 GS. Twelve patients deceased after ASCT. Nine patients died of relapsed lymphoma at a median of 10 months (range: 6-43 months) post-ASCT. Three patients died of myelodysplastic syndrome/ acute myeloid leukemia (MDS/AML) at 15, 36 and 42 months post-ASCT. All three were lymphoma-free at the time of death and all had true-negative at D-100 GS.

Table 1
Pathologic radiogallium distribution and pathologic computed tomography findings of the patients

	D-100 follow-up			D-200 follow-up		
	n	Abnormal	Normal	n	Abnormal	Normal
Ga-67 scintigraphy	40	15	25	15 (1 PET)	8	7
Computed tomography	40	16	24	19	8	11

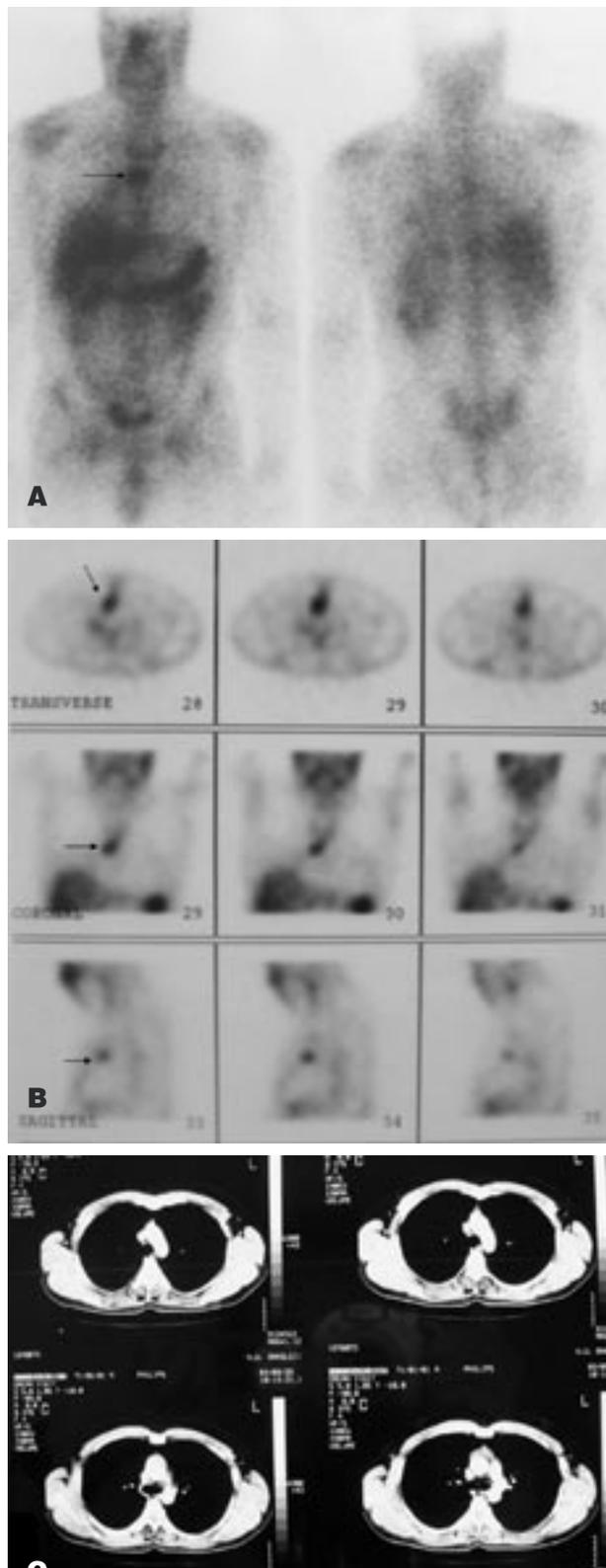


Fig 1 (A,B,C). A 32-year-old male patient with the diagnosis of NHL relapsed and he was decided to undergo ASCT. (A,B): A whole body Ga-67 scintigraphy performed 100 days after ASCT showed focal uptake of radiogallium in the thorax, located in the pretracheal area on the thorax SPECT images (arrow). (C): CT study showed no abnormality. He died on the follow-up at 6 months due to progressive disease

Prediction of D-100 GS on survival in lymphoma patients post-ASCT is evaluated by Kaplan-Meier analysis (Figure 3A). Three patients who died of MDS/AML were not included in the survival analysis. In 85.7% of the patients who had a negative GS at D-100 were disease-free and alive whereas only 28.6% of the patients who had a positive GS were disease-free and alive at a median follow up of 30 months (range: 6-61 months) ($p=0.005$). On the other hand, assessment of D-100 CT did not predict survival of lymphoma patients post-ASCT (Figure 3B). Of the patients 64.4% with a negative CT scan at D-100 were disease-free and alive whereas 57.7% with a positive CT scan were disease-free and alive at a median follow up of 30 months (range: 6-61 months) ($p=0.12$).

The PPV, NPV and accuracy for GS were 64%, 88% and 77.5%, respectively. The same values for CT were PPV: 37.5%, NPV: 75% and accuracy: 60%.

DISCUSSION

Depending on the histology and risk factors, 30% to 75% of patients with advanced HD and aggressive NHL can be cured with front-line treatment (1). However, patients who do not achieve complete remission (CR) at the end of first-line treatment or who have a relapse after CR, have a poor prognosis regardless of any further conventional treatment (1). Treatment with high-dose chemotherapy combined with stem cell transplantation increases survival (2-5) and response to treatment is currently assessed on the basis of clinical, radiologic, and pathologic criteria. Computed tomography remains the standard for the evaluation of nodal disease. However, defining response criteria based on conventional radiographic characteristics remains difficult because lymphoma patients treated with chemotherapy often present with residual masses of uncertain significance. These residual masses may consist of fibrotic tissue or viable tumor and CT cannot differentiate between active tumor and fibrosis (11). In the management of lymphoma, GS has been used with some success in differentiating residual disease from fibrotic masses after treatment (11,12). Role of GS in the follow-up has been studied immensely as well, all showing better performance over CT (11,12). However, few studies have been conducted on the value of GS after high dose chemotherapy and ASCT. In this study, GS obtained before and 100 days after high dose chemotherapy in addition to ASCT were compared with CT scans within the same time intervals. The predictive value of the scans was evaluated for these patients as well.

The follow-up of 25 patients with normal GS findings on D-100 post-ASCT revealed that they were all in CR, except 3. One of them had normal findings on GS and CT, both on D-100 and D-200, developed MDS and was lost

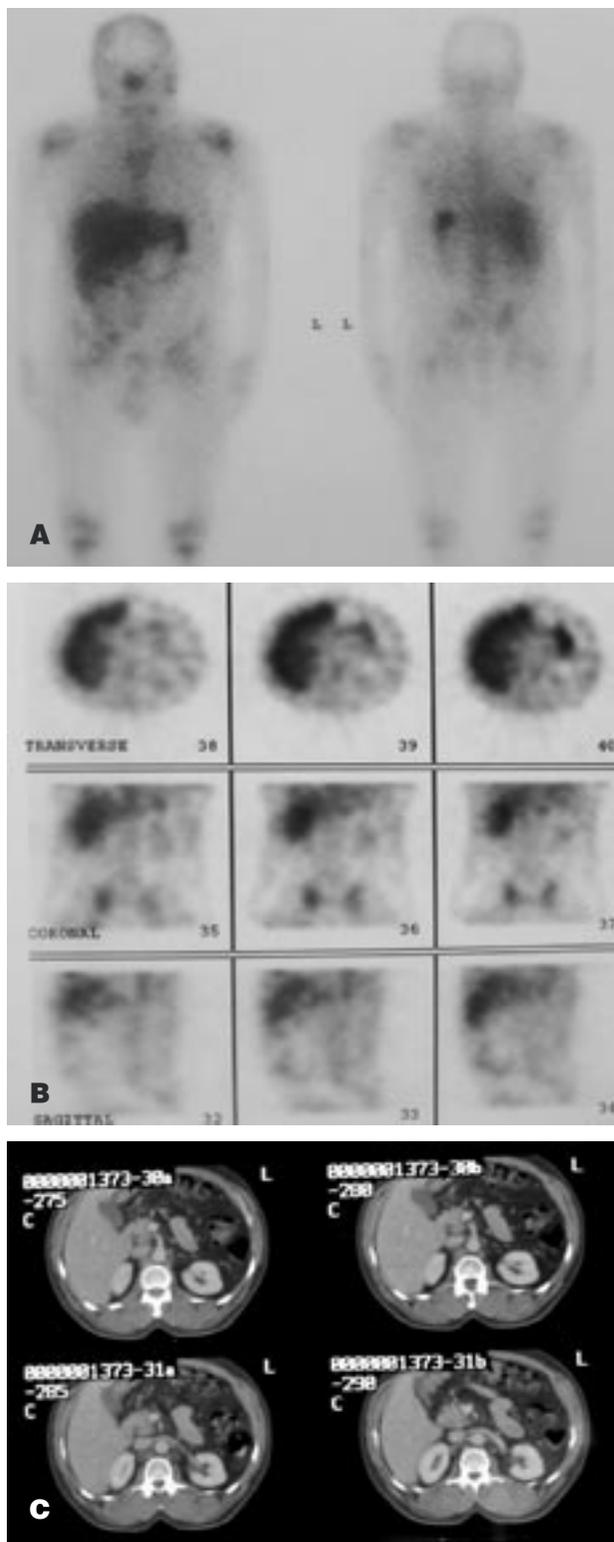


Fig 2 (A,B,C). A 46-year-old male patient with relapsed follicular B cell NHL had undergone high dose chemotherapy followed by ASCT. (A,B): His planar Ga-67 whole body scintigraphy and SPECT images of the abdomen performed at day 100 post-transplantation showed normal distribution of the activity. (C): CT study showed lymph nodes (the largest measuring 22x23 mm) located in the paraaortic, paracaval area around the celiac truncus. He was followed-up for 34 months and was in clinical complete remission

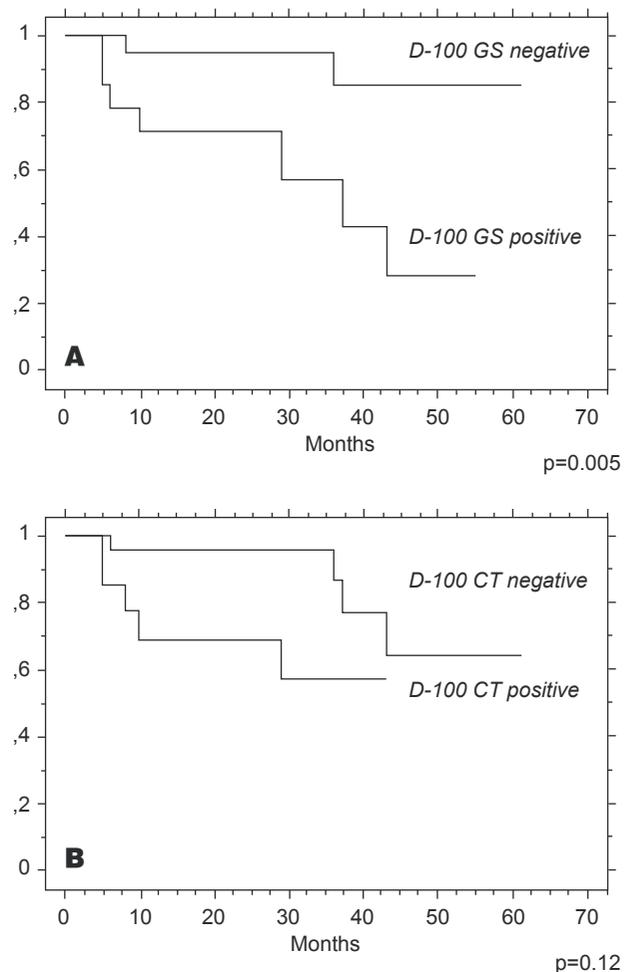


Fig 3 (A,B). Kaplan-Meier survival curves depicting the progression free survival of lymphoma patients according to GS (A) and CT (B) results after ASCT

eventually on 42 months post-ASCT. The second patient who developed acute myeloid leukemia and died 40 months post-ASCT, had normal GS but abnormal CT findings in the pretracheal area but these lesions disappeared in the control CT scans on D-200. The last patient had normal Ga-67 and CT scan, relapsed 18 months later and died 36 months post-ASCT. So this patient was considered false negative of GS, but to the best of our knowledge there is no knowledge of how long a GS could predict event free survival.

Written reports of CT and GS were used to establish the predictive values of these tests. Using written reports might have put GS at a relative disadvantage compared to conventional imaging due to the diverse experience of the readers for the distribution of Ga-67 in the body. Pitfalls in the interpretation of GS are very well established, because of various reasons (12). The false positive results in this study is mainly due to the prominent hilar uptake of Ga-67, which is usually seen in patients with a history of cigarette smoking, and after cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP)

chemotherapy regimens. Although bilateral mild hilar uptake, which is less than the original disease, of Ga-67 is very well described in the literature (13) sometimes as in this study asymmetrical severe uptake can be misleading. Asymmetrical uptake of Ga-67 not only in the hilar region but also in the breast came up to be false positive on the follow-up clinically as well.

GS is being replaced by a newer technique in centers that have the appropriate facilities for FDG imaging. As in the case of Ga-67, FDG is a tumor viability agent and its uptake indicates the presence of active disease (14,15). FDG has already been found to overcome some of the limitations of GS in the evaluation in lymphoma patients. However, dedicated FDG-PET is currently still of limited availability. SPECT systems are commonly used in the routine practice of nuclear medicine. The limitations and pitfalls of GS have been elaborated in large number of patients and currently do not interfere with image interpretation by physicians with appropriate knowledge and expertise. GS is a good functional imaging modality for lymphoma, it may detect relapse earlier than conventional imaging modalities and identifies patients with refractory disease. The current study demonstrates

that GS can be used to predict the outcome of patients undergoing ASCT with lymphoma accurately. In contrast, CT was unable to reliably predict disease-free survival, mainly due to its poor specificity. We hope that our data regarding the use of GS in the evaluation of patients with lymphoma undergoing ASCT is useful and is added to the list of GS utilization list.

CONCLUSION

D-100 Gallium scintigraphy is an important additional imaging modality to aid in the decision whether to administer therapy post-transplantation, particularly when conventional imaging is ambiguous or inconclusive and there is a significant clinical suspicion of relapsing disease. A negative GS in this scenario is useful in confirming that therapy administration is not required. If GS is equivocal and biopsy is not possible, a repeat GS at 200 days post-transplantation is helpful in clarifying whether disease is present. The prognostic accuracy of GS is superior to that of conventional CT imaging; therefore, GS can be the imaging modality of choice for predicting the outcome of patients with aggressive lymphoma eligible for ASCT in centers where PET scanning is not available.

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