Beta-2 Microglobulin as a Diagnostic Parameter in Non-Hodgkin Lymphoma: A Comparative Study with FDG-PET

DANIEL F. TOTH[1], MARKUS RADERER[2], WOLFGANG WADSAK[1] and GEORGIOS KARANIKAS[1]

Departments of [1]Radiology and Nuclear Medicine, and [2]Internal Medicine, Division of Oncology, Medical University of Vienna, Vienna, Austria

Abstract. *Aim: The aim of this study was to determine the diagnostic value of the serum tumor marker beta-2 microglobulin (β2M) as well as positron emission tomography (PET) using ^{18}F-fluorodeoxyglucose (FDG) in confirming or eliminating the diagnosis of non-Hodgkin lymphoma (NHL). Patients and Methods: Retrospective analysis of 180 patients with NHL referred for a PET scan was performed. Patients' data regarding demographic information, clinical history, and diagnostic procedures were collected. The sensitivity, specificity, and positive/negative predictive value of serum β2M levels and FDG-PET, compared to a compound gold standard consisting of imaging modalities (computed tomography, magnetic resonance tomography, ultrasound) and/or biopsy, were assessed and compared. Results: β2M had a sensitivity and specificity of 49% and 52% for all types and settings, respectively, as well as a low positive predictive value (66%) and a very low negative predictive value (36%). The overall sensitivity and specificity of FDG-PET for all types of NHL in all settings was 87% and 92%, respectively. Conclusion: Due to its low sensitivity and specificity, β2M cannot be used in the clinical routine as a diagnostic marker for the diagnosis of NHL. On the other hand, in accordance with previous studies, we found that FDG-PET is an excellent tool for the diagnosis of NHL.*

Lymphomas account for nearly 5% of all new cancer cases in the USA, 90% of which are non-Hodgkin (NHL) in type (incidence: 16/100,000). The disease is fatal for approximately 30% of all patients with NHL, and thus accounts for 19,500 deaths per year, or about 3.5% of all cancer deaths nationwide (1). A timely diagnosis is of great importance, as early therapy significantly improves outcomes and survival (2, 3).

Correspondence to: Professor Dr. Georgios Karanikas, Waehringer Guertel 18-20, A-1090 Vienna, Austria. E-mail: georgios.karanikas@meduniwien.ac.at

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The clinical use of positron emission tomography (PET) with ^{18}F-fluorodeoxyglucose FDG for diagnosis, staging, treatment monitoring, and detection of disease recurrence in patients with a number of cancer types is established and has been evaluated by a number of studies (4-15), including some for NHL (16-21).

In general, except for a subgroup of patients with low-grade NHLs, most cases of NHL have a high uptake of FDG and are accordingly well-suited for detection using PET. In most studies that have compared the efficiency of PET with conventional imaging [contrast-enhanced computed tomography (CT), magnetic resonance imaging (MRI)], PET was found to be superior, with PET having a sensitivity of about 10% higher than CT, a specificity of up to 50% higher, resulting in relevant changes in staging in 10% of cases (16-21).

Beta-2 microglobulin (β2M) is a human leukocyte antigen-class I molecule. β2M can be measured in serum and plasma, and can function as a tumor marker for several types of solid and hematological malignancies, including multiple myeloma and lymphoma, both Hodgkin and non-Hodgkin type (22). Its pre- and post-treatment prognostic value has been examined in several studies and high correlations have been found between levels of β2M and survival time, with high levels correlating with shorter survival (22-25).

Although these studies have tried to determine the prognostic value of β2M in NHL, to our knowledge, no reports have assessed the diagnostic value of this tumor marker to date. The aim of this study was to determine the diagnostic value of the serum tumor marker β2M, as well as FDG-PET, in confirming or eliminating the diagnosis of NHL.

Patients and Methods

Patients. This study was approved by the Ethics Committee of the Medical University of Vienna (EK 054/2012).

Between February 1998 and December 2009, a total of 1,100 patients underwent FDG-PET examinations for the purpose of staging, re-staging, or follow-up of NHL. All patients who underwent a PET scan had a confirmed biopsy of some subtype of NHL at some point in their medical history. Only patients with sufficient documentation were included in this study. For every FDG-PET examination performed, serum β2M values were required

within a time frame of one week (unless they were unavailable within one week; maximum of four weeks if no therapy was given in the meantime) from the FDG-PET scan.

As the gold standard for verification of NHL, histological assessment from biopsy (disease sites: lymph nodes or bone marrow), or diagnostic modalities such as CT, MRI, or ultrasound, were required within the same time frame as above. Whenever relevant biopsy results were available, they superseded imaging results. No further exclusion criteria were set. A total of 180 out of 1,100 patients fulfilled all the criteria and were included in the present study (n=180; 103 male patients and 77 female patients; mean age=50.5 years±15.6 years; range=17-83 years).

The reference value at the laboratory used for β2M is given as <1.9 mg/l, *e.g.* any value of 1.9 mg/l or higher is considered pathological. A positive PET result was defined as requiring the presence of abnormal glucose uptake in relevant areas, while a negative PET result was the absence of any such uptake. If no clear determination was made, the PET was rated as inconclusive. Reasons for this included only very minimal changes in glucose uptake, insufficient data acquisition or patient preparation (such as an overly long interval between tracer application and image acquisition), insufficient fasting, or artifacts due to movement.

The results of the FDG-PET scan were determined by individual physicians (experts in the field of nuclear medicine) at the time that the examination was performed. For our analysis, these reports were used and were not additionally verified.

Statistical analysis. Statistical planning and analysis for this study were performed using IBM SPSS Statistics (IBM, Version 19.0; Armonk, NY, USA). With the acquired data, the sensitivity, specificity, and positive and negative predictive value of FDG-PET scans, as well as β2M, were calculated in comparison to the gold standard described above. Sensitivity was calculated as the quotient of true-negatives and the sum of true-negatives and false-positives; specificity as the quotient of true-positives and the sum of true-positives and false-negatives; positive predictive value (PPV) as the quotient of true positives and the sum of both true and false positives; and negative predictive value (NPV) as the quotient of true-negatives and the sum of both true- and false-negatives.

Results

Four patients out of the 180 in the study group did not have exact histological classifications and were merely reported to have some form of NHL. The total number of patients with diffuse large B-cell lymphomas (DLBCL), including primary mediastinal and other localizations, was 97, which corresponds to 53.9%. The next largest group of lymphomas was of the follicular type at 18.3% (33 patients) and mantle cell lymphoma at 7.8% (14 patients). The remainder was made up of mucosa-associated lymphoid tissue lymphoma (nine patients), anaplastic large cell lymphoma (seven), peripheral T-cell lymphoma (six), precursor T-cell leukemia/lymphoma (four), Burkitt lymphoma (three) and nodal marginal zone lymphoma (three).

Examinations. The median serum level for β2M in the study group was 1.88 mg/l. The highest recorded value was 17.8 mg/l, while the lowest was 0.77 mg/l. In summary, 93 patients had positive and 87 had negative β2M results (Figure 1).

The study group of 180 patients underwent a total of 645 FDG-PET scans for an average of 3.6 examinations per patient. At 53.0%, the majority of these scans were performed for re-staging, 35.5% for follow-up and 11.5% for staging. None of the examinations were performed for treatment monitoring.

In the follow-up setting, continuing remission was established using FDG-PET in 67.7% of cases, while relapse was found in 23.2% of patients, and no clear answer was provided in the remaining 9.2%. As for re-staging, 35.1% of patients were disease-free as far as glucose uptake could determine, while 57.6% still had active disease present. Out of these, the activity and localizations of pathologic glucose uptake remained constant in 28.1%, progressed in 15.8% and regressed in 13.7% of patients. In 7.31% of patients, the results of the PET scan were inconclusive. Finally, in the staging setting, 86.5% of patients were indeed found to have metabolically active tumor tissue present, while for 6.76% of patients, findings were negative or inconclusive. In total, FDG-PET was not helpful for determining tumor activity in 7.9% of all scans (see Table I).

Comparison of results. The results of serum β2M values compared to the gold standard can be found in Table II. The results were concordant (both positive or both negative) in 92 cases out of 180, resulting in an accuracy of 51.1%. Out of the remaining 48.9% of cases, 32 were false-positive (for a false-positive rate of 50.8%) and 56 were false-negative (for a false-negative rate of 47.9%). This gives the serum β2M values in this study a sensitivity of 49.2% and a specificity of 52.1%, respectively, as well as a PPV of 65.6% and a NPV of 35.6%.

The results of the FDG-PET scan compared to the gold standard can also be found in Table II. The results were concordant (both positive or both negative) in 443 cases out of 492, resulting in an accuracy of 90.0%. Out of the remaining 10% of cases, 27 were false-positives (for a false-positive rate of 12.8%) and 22 were false-negatives (for a false-negative rate of 7.8%). Accordingly, the sensitivity of FDG-PET was 87.2% and the specificity was 92.2%; the PPV was 90.6% and the NPV was 89.3%.

For a closer look, a division into several sub-entities was made. The three groups of histological types for this purpose are diffuse large B-cell lymphoma (including primary mediastinal DLBCL), follicular lymphoma, and all other subtypes. The sensitivity and specificity in these settings were 84.2% and 91.6% for DLBCL, 90.6% and 94.4% for follicular lymphoma and 91.5% and 91.7% for other types, respectively (see Table III).

When cases were divided by reason for referral, the sensitivity and specificity were 95.6% and 81.6% for follow-up, 84.5% and 93.0% for restaging, and 45.6% and 98.3% for staging, respectively.

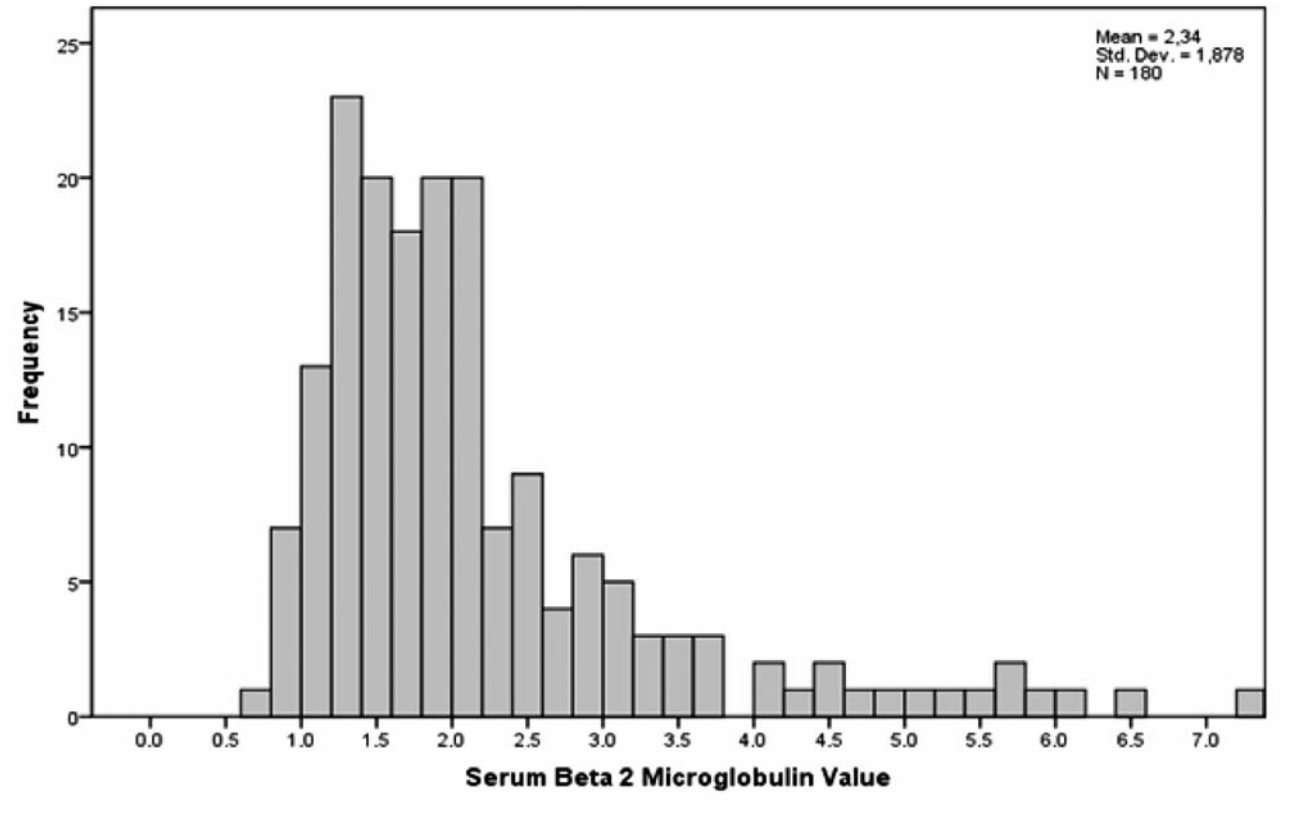

Figure 1. *Results of serum beta-2 microglobulin assay. Histogram of distribution of serum levels.*

Discussion

Despite advances in imaging, the diagnosis of NHL still poses a problem. An accurate confirmation or exclusion of active disease is important as, with modern treatment options, many patients with NHL can now be permanently cured. Likewise, an early detection of relapse will more likely lead to a better patient outcome.

Several studies have shown that FDG-PET may be especially useful in detecting lymphoma, a hematological disorder which is not necessarily confined to a certain area, but may be present in different parts of the hematopoietic and lymphatic system simultaneously. Its usefulness for finding occult disease sites has been confirmed (16-21). β2M is a tumor marker for several malignancies, including NHL, and its prognostic value has been confirmed by several studies (22-25).

In this study, we examined the performance of both FDG-PET and of the serum tumor marker β2M for the diagnosis of NHL.

The gender distribution of the study group was biased slightly towards males at 57%. This number is in accordance with the figures provided by the American Cancer Society, who found that just over half (55%) of all new cases in 2009 were males. (1)

The median age of the study group was unusually low, at just over 50 years (median=52 years, mean=51 years). The National Cancer Institute's Surveillance Epidemiology and End Results (SEER) database provides a median age of 66 years. The reasons for this are not entirely clear, but we hypothesize that oncologists at our institution might be more likely to perform a higher number of re-staging and follow-up scans in younger patient populations, where therapy might also be more aggressive.

As for the distribution of histological subtypes, DLBCL compromised by far the largest group at 54%, when primary mediastinal DLBCL is included. This is an unusually high proportion compared to the incidence of 33% reported in the introduction (1). The reasons for this are unknown, although it seems plausible that patients with this subtype are more commonly referred for FDG-PET scans due the perceived or expected higher sensitivity of the scan in this highly active and therefore marker-avid tumor class. Furthermore, oncologists might be monitoring therapy results more closely, as changes are more rapid than in indolent tumor classes.

Follicular cell lymphoma made up 18% of the study group (*vs.* 22% in the population). The other subtypes of NHL made up a similar percentage of the study group as in the general population.

Table I. *Results of fluorodeoxyglucose-positron emission tomography by finding, grouped by reason for referral.*

FDG-PET results		Indication for scan			
		Follow-up	Restaging	Staging	Total
Result	Negative	155 (67.7%)	120 (35.1%)	5 (6.76%)	280 (43.4%)
	Inconclusive	21 (9.17%)	25 (7.31%)	5 (6.76%)	51 (7.91%)
	Positive (all)	53 (23.2%)	197 (57.6%)	64 (86.5%)	314 (48.7%)
	- Stable		96 (28.1%)	64 (86.5%)	160 (24.8%)
	- Regressive		47 (13.7%)		47 (7.29%)
	- Progressive	53 (23.2%)	54 (15.8%)		107 (16.6%)
	Total	229 (35.5%)	342 (53.0%)	74 (11.5%)	645

β2M proved to have a low sensitivity (49%) as well as specificity (52%) and low PPV (66%) as well as NPV (36%). This leads to the assessment that absolute values of β2M are not suited for the confirmation or exclusion of active NHL.

β2M is often used as a prognostic factor and its use as such is highly validated in studies (23-25). Unfortunately, the clinical information system at our institution did not provide sufficient data (*e.g.* date of death) to assess survival times, as these could have been compared to FDG-PET data to determine whether certain markers in PET [overall result, progression, highest relevant standard uptake value (SUV), change in highest relevant SUV] could also be useful prognostic markers. We would, therefore, recommend a carefully planned and designed prospective study to answer this question.

Our results were able to confirm the usefulness of FDG-PET for the diagnosis of NHL. The performance of FDG-PET was comparable to that of other studies and meta-analyses on this topic. In this study, the overall sensitivity and specificity for all types of NHL and in all situations (staging, re-staging, and follow-up) was 87% and 92%, respectively, for an accuracy of 90%. This is comparable to these found in other large studies [71% and 90%, and 83% to 100%, respectively (9, 17, 18)]; FDG-PET performed better in follicular lymphoma (sensitivity 90% and specificity 94%) than in DLBCL (sensitivity 84%, specificity 92%) or other types of lymphoma.

FDG-PET had a very high specificity in the re-staging (93%) and staging (98%) situations, but a comparatively low specificity in follow-up (81%). Conversely, it had a very high sensitivity in follow-up (95%), but relatively lower sensitivity in restaging (84%) and poor sensitivity in staging (55%). This is in line with many publications that recommend the usage of FDG-PET for re-staging and follow-up, but not for staging. No patients in the study group were referred for therapy monitoring, so this situation could not be examined.

Limitations

This study has several limitations. Due to its retrospective design, this study is limited to the evaluation of the diagnostic process, and therapeutic consequences were not assessed.

Table II. *Results of serum beta-2 microglobulin (β2M) assay as well as fluorodeoxyglucose-positron emission tomography scans, compared with gold standard results (absolute numbers).*

		Gold standard		
		Positive	Negative	Total
β2M result	Positive	61	32	93
	Negative	56	31	87
	Total	117	63	180
PET result	Positive	259	27	286
	Negative	22	184	206
	Total	281	211	492

Furthermore, a better role for β2M may be as parameter of progression that can show whether disease in a specific person has become less or more active, when current values are compared to previous (*e.g.* pre-treatment) values. However, this is only theoretical as the design of this study was not suited to test this question, since only one value for β2M per patient was recorded.

Conclusion

According to our data, β2M is not at all a reliable marker for diagnosis of NHL and has no use in this setting. Although it is useful as a prognostic marker in staging, we do not recommend determining it in re-staging or follow-up.

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Table III. *Results of fluorodeoxyglucose-positron emission tomography scan compared with gold standard, grouped by histological subtype of NHL (absolute numbers).*

		Gold standard		
		Positive	Negative	Total
PET result				
Diffuse large B-cell lymphoma	Positive	142	19	161
	Negative	13	101	114
	Total	155	120	275
Follicular lymphoma	Positive	51	3	54
	Negative	3	29	32
	Total	54	32	86
Other type	Positive	66	5	71
	Negative	6	54	60
	Total	72	59	131

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