

Hemato-oncology Tourism in Israel: A Retrospective Review

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abstract

PURPOSE Despite the significant increase in medical tourism worldwide, data on medical tourist (MT) clinical characteristics and treatment outcomes are lacking. Many MTs who choose Israel to receive medical services are individuals diagnosed with hematologic malignancies. The purpose of this study was to describe hemato-oncology MTs and to compare their disease characteristics and treatment outcomes to a control group of local (Israeli) hemato-oncology patients.

MATERIALS AND METHODS In this retrospective review, we analyzed hospital records of all hemato-oncology tourists and Israeli patients diagnosed and/or treated at the Institute of Hematology, Assuta Medical Center, between 2014 and 2016. MT and local patient demographics, clinical characteristics, and treatment outcomes were compared. MT data were also analyzed according to their commitment to treatment in Israel.

RESULTS Data on 110 MTs (median age, 51.0 years; 53.6% women) and 122 local patients (median age, 65.0 years; 41.8% women) diagnosed with non-Hodgkin lymphoma (NHL), Hodgkin lymphoma, and multiple myeloma were analyzed. The most common hematologic malignancy in both MTs and local patients was NHL (54.5% and 73.0%, respectively). Among MTs, 32.7% were fully committed to treatment in Israel, 32.7% were partially committed, and 34.6% were not committed. In 25.9% of MTs, a review of their biopsy resulted in a more definitive or different diagnosis. The percentage of patients who achieved complete response to treatment was similar among MTs and local patients.

CONCLUSION MTs often require a pathologic review of their initial diagnosis and are more likely to present with advanced stages of disease. Treatment of MTs according to the appropriate clinical parameters is expected to yield similar outcomes to those of local patients.

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INTRODUCTION

In a globalizing world, medical services are no longer confined to national borders, as millions of people take advantage of high-quality and affordable medical services available abroad.^{1,2} This is also the case in Israel, in which the provision of medical tourism services has been on the rise over the past two decades.³

Despite the increasing market share of medical tourism, most of the studies that have investigated this phenomenon have focused on its economic potential,^{4,5} political aspects,^{6,7} or ethical issues,⁸ whereas information on patient clinical characteristics and outcomes is lacking.⁹ Many medical tourists (MTs) who choose to come to Israel are hemato-oncology patients pursuing accurate and fast diagnosis and reliable treatment and results outside of their country of origin.³ Some MT patients stay in Israel after being diagnosed to receive the recommended

treatment plan; others stay for a maximum of one cycle of treatment, if at all; and the rest combine treatments in Israel and in their home country. However, changes to the treatment plan may have major implications on treatment outcomes.

The aims of the current study were to describe the disease characteristics and treatment outcomes of hemato-oncology MTs who were treated at a private medical center in Israel and to compare them to those of local (Israeli) patients who were diagnosed with hematologic malignancies and treated at the same center.

MATERIALS AND METHODS

Patients and Setting

This retrospective analysis included medical records of all consecutive MTs and local patients who were diagnosed with non-Hodgkin lymphoma (NHL), Hodgkin lymphoma (HL), and multiple myeloma (MM) and

Author affiliations and support information (if applicable) appear at the end of this article.

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CONTEXT

Key Objective

Despite the significant increase in medical tourism worldwide, data on the clinical characteristics and treatment outcomes of medical tourists (MTs) are lacking. What are the clinical characteristics of hemato-oncology MTs, and are they different from those of local patients?

Knowledge Generated

Hemato-oncology MT patients are more likely to present with advanced stages of disease as compared with local patients and often require a pathologic review of their initial diagnosis.

Relevance

Treating according to appropriate clinical parameters is expected to yield similar treatment outcomes in MTs compared with those of local patients.

received consultation and/or were treated at the Institute of Hematology at Assuta Medical Centers (AMCs; Israel) at least once between 2014 and 2016. The study was approved by the local institutional ethics committee. We compared the clinical characteristics and treatment outcomes of MTs and local (Israeli) patients who were diagnosed with the same malignancies and who were treated at least once at the Institute of Hematology during the same period.

Hemato-oncology MTs were also categorized according to their commitment to the recommended treatment plan devised by the Institute of Hematology, as follows:

1. Fully committed patients were those who received the entire recommended treatment plan in Israel.
2. Partially committed patients were those who combined treatments in Israel and their home country.
3. Noncommitted patients were those who were treated in Israel for a maximum of one cycle, if at all.

Regardless of their commitment type, MTs could return to AMC at the end of their treatment for evaluation of their medical condition.

Study Measures

Information on sociodemographics, histologic diagnosis, management, and treatments provided in Israel was meticulously collected from the patients' medical records. In addition, MT mortality information was collected from their medical records and MT agencies. All histologic diagnoses were reviewed by a local senior hematopathologist.

The duration of follow-up was calculated for each patient according to the number of days between the first and last visit to AMC. Treatment response rates were defined according to Response Evaluation Criteria in Lymphoma 2017¹⁰ for patients with lymphoma and according to International Myeloma Working Group guidelines¹¹ for patients with MM. Response rates were calculated for local patients and MTs who were assessed at AMC after completing their treatment.

Data Analysis

The SPSS statistical package (Version 25; IBM, Armonk, NY) was used for all statistical analyses. Continuous variables were summarized using the median and interquartile range (IQR), and categorical variables were summarized using numbers and percentages. The 1-sample Kolmogorov-Smirnov test and histogram with normal curve were used to assess normal distributions of continuous variables.

Comparisons between hemato-oncology MTs and local patients were performed using the χ^2 test for categorical variables and the Mann-Whitney *U* test for nonnormally distributed continuous variables. Comparisons among hemato-oncology MT subgroups were performed using the χ^2 test for categorical variables and the Kruskal-Wallis test for nonnormally distributed continuous variables.

Multivariable logistic-regression analysis was adjusted for potential confounding factors (ie, age and disease stage), and odds ratios and their 95% CIs were calculated. All results were corrected for multiple comparisons and were considered significant if the false discovery rate (FDR) was < 0.05 .

RESULTS

Characteristics of the Study Population

A total of 110 hemato-oncology MTs and 122 local patients were included in the analysis. Most tourists were from Russia (60 of 110 MTs; 54.5%) and the Ukraine (30 of 110 MTs; 27.3%); the rest came from Kazakhstan, Qatar, Azerbaijan, Georgia, and Uzbekistan (Fig 1).

No statistically significant sex differences were observed between MTs and local patients (59 [53.6%] of 110 MTs were women *v* 51 [41.8%] of 122 local patients). Only MTs with NHL were significantly younger than local patients with NHL (median age, 54.5 years [IQR, 40.2-64.2 years] *v* 65.0 years [IQR, 58.0-73.0 years], respectively; FDR < 0.001), whereas no age difference was noted between MTs and local patients with HL (median age, 31.0 years [IQR, 25.0-43.3 years] *v* 41.0 years [IQR, 24.0-47.0 years],

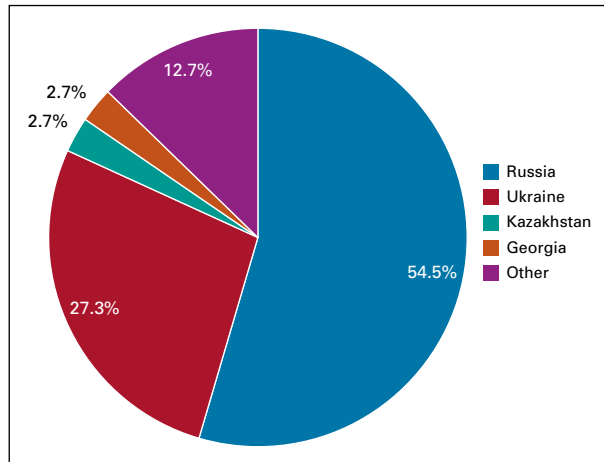


FIG 1. Country of origin of hemato-oncology medical tourists who were diagnosed and/or treated at Assuta Medical Centers between 2014 and 2016. Other includes Azerbaijan, Tanzania, Uzbekistan, and Qatar.

respectively) or MM (median age, 62.0 years [IQR, 55.5-65.2 years] v 66.5 years [IQR, 58.8-73.0 years], respectively).

More than half of the MTs (64 of 110 MTs; 58.2%) were diagnosed with a known or suspected malignancy in their home country. The most common diagnoses were follicular lymphoma (30 of 110 MTs; 46.9%) and diffuse large B-cell lymphoma (DLBCL; 19 of 110 MTs; 29.7%). A significantly higher percentage of noncommitted MTs were diagnosed in their home country, compared with partially and fully

committed patients (80.6% v 54.5% and 47.2%, respectively; FDR = 0.025).

Of the 64 MTs with a known or suspected diagnosis, 54 (84.4%) had a histologic specimen available for a histologic review by a senior hematopathologist at AMC. The histologic review fully confirmed only 74.1% of the diagnoses (40 of 54 MTs). The original diagnosis was completely revised in five MTs, whereas a definitive diagnosis was suggested in nine MTs who were suspected as having malignant disease (without a definitive diagnosis) in the MT's home country (Table 1)

Disease Characteristics

The most frequent hematologic malignancy in both study groups was NHL, which was diagnosed in 54.5% of MTs (60 of 110 MTs) and in 73% of local patients (89 of 122 local patients). HL was the second most frequent hematologic malignancy among MTs (36 of 110 MTs; 32.7%), whereas MM was the second most frequent hematologic malignancy in local patients (26 of 122 local patients; 21.3%). The proportion of patients with HL was significantly higher among MTs than local patients (36 [32.7%] of 110 MTs v 7 [5.7%] of 122 local patients; age-adjusted FDR > 0.001; Fig 2). Although the proportions of patients with NHL and MM were lower among MTs compared with local patients, these differences were not statistically significant (Fig 2).

The most common type of NHL among MTs was DLBCL (42 of 60 MTs; 70.0%), whereas among local patients, the

TABLE 1. Original and New Diagnoses of Medical Tourists With an Available Histologic Specimen

Serial No.	Original Diagnosis	New Diagnosis	Medical Tourist Commitment to Treatment
Revised diagnosis			
19	Diffuse large B-cell lymphoma	Hairy cell leukemia	Noncommitted
108	Anaplastic lymphoma	Hodgkin lymphoma	Noncommitted
79	Non-Hodgkin lymphoma	Hodgkin lymphoma	Partially committed
60	Lymphoma	Chronic lymphocytic leukemia	Partially committed
9	Pancreatic carcinoma	Diffuse large B-cell lymphoma	Fully committed
Definitive diagnosis ^a			
27	High suspicion of malignancy without a definitive diagnosis	Diffuse large B-cell lymphoma	Noncommitted
80	High suspicion of malignancy without a definitive diagnosis	Hodgkin lymphoma	Noncommitted
36	High suspicion of malignancy without a definitive diagnosis	Diffuse large B-cell lymphoma	Partially committed
103	High suspicion of malignancy without a definitive diagnosis	Hodgkin lymphoma	Partially committed
109	High suspicion of malignancy without a definitive diagnosis	Hodgkin lymphoma	Fully committed
101	High suspicion of malignancy without a definitive diagnosis	Hodgkin lymphoma	Fully committed
40	High suspicion of malignancy without a definitive diagnosis	Diffuse large B-cell lymphoma	Fully committed
89	High suspicion of malignancy without a definitive diagnosis	Hodgkin lymphoma	Fully committed
104	High suspicion of malignancy without a definitive diagnosis	Hodgkin lymphoma	Fully committed

^aDefinitive diagnosis indicates when the pathologist from the country of origin was unable to diagnose the disease and a definitive diagnosis was made after biopsy review at Assuta Medical Centers.

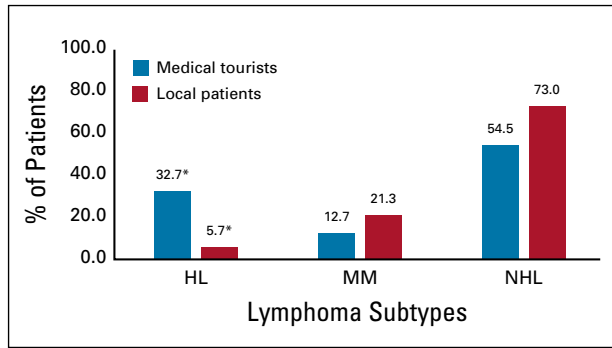


FIG 2. Distribution of lymphoma malignancies among medical tourists and local patients. Data were available for 110 medical tourists and 122 local patients. (*) Age-adjusted false discovery rate = 0.003. HL, Hodgkin lymphoma; MM, Multiple myeloma; NHL, non-Hodgkin lymphoma.

proportions of patients with DLBCL and chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) were similar (35 of 89 local patients; 39.3%). After adjusting for age, the proportion of patients with CLL or SLL was significantly different between MTs and local patients (age-adjusted FDR = 0.001; Fig 3).

A higher percentage of MTs, specifically patients with MM, were diagnosed at advanced stages of the disease (stage III or IV) compared with local patients, although this was borderline statistically significant (age-adjusted FDR = 0.068; Table 2). A significantly higher percentage of MTs with NHL had B symptoms compared with local patients.

A subanalysis among MTs who were diagnosed in their home country showed that the median number of days from initial diagnosis in their home country to the first visit at AMC was significantly longer among MTs who were diagnosed with more advanced stages (stage III or IV) at AMC (n = 22; median, 109.0 days; range, 0.0-216 days) compared with MTs who were diagnosed with less

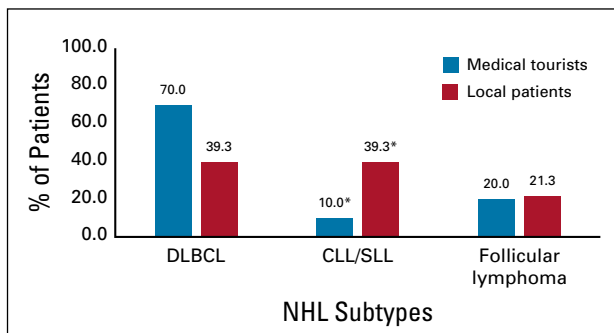


FIG 3. Distribution of non-Hodgkin lymphoma (NHL) subtypes among hemato-oncology medical tourists and local patients. Data were available for 110 medical tourists and 122 Israeli patients. (*) Age-adjusted false discovery rate = 0.001. CLL, chronic lymphocytic leukemia; DLBCL, diffuse large B-cell lymphoma; SLL, small lymphocytic lymphoma.

advanced stages (stage I or II) at AMC (n = 36; median, 53 days; range, 3.0-390 days; $P = .022$)

Commitment to Treatment Among MTs

MTs were distributed almost equally among the 3 commitment to treatment categories; 38 MTs (34.5%) were noncommitted, 36 (32.7%) were partially committed, and 36 (32.7%) were fully committed. Demographic characteristics (age, sex, and country of origin) were not significantly different among these subgroups. The rate of commitment to the recommended treatment plan was similar within lymphoma and NHL subtypes.

Mortality data were available on 44 MTs (40%). No significant differences in mortality rates were found among noncommitted, partially committed, and fully committed MTs (0 of 5, 2 of 17, and 0 of 22 MTs, respectively; $P = .42$). In addition, there were no significant differences among these subgroups regarding disease stage at diagnosis and the onset of B symptoms.

Treatment Characteristics and Response

A significantly higher percentage of MTs than local patients received at least 1 treatment cycle before their first visit to AMC (25.5% v 10.7%, respectively; age-adjusted FDR = 0.048). This rate was particularly high among noncommitted MTs (17 of 37 noncommitted MTs; 45.9%).

The median follow-up period in Israel was five times shorter among MTs compared with local patients (110.0 days [IQR, 8.0-303.5 days] v 581.0 days [IQR, 141.0-850.0 days], respectively; age- and disease stage-adjusted FDR < 0.001). Similar trends were observed in each of the disease subgroups, although not all were statistically significant, probably as a result of the subgroups' small size (Table 2).

At the end of treatment, information on treatment response was available for 61 MTs (30 fully committed, 23 partially committed, and 8 noncommitted MTs) and 97 local patients (Table 2). After adjusting for age and disease stage, the percentage of patients who achieved complete response was similar in MTs and local patients (57.4% v 39.2%, respectively; FDR = 0.510). The percentage of patients who achieved a complete response was also similar among the MT subgroups.

DISCUSSION

Medical tourism is a rapidly growing world trend with a great potential; however, its clinical characteristics are not well studied. The main objective of this retrospective review was to provide a better understanding, especially from a clinical perspective, of the hemato-oncology MTs who received health services at AMC.

The main finding of this study is that the pathologic review of MT biopsies contributed to these patients' diagnosis. Consequently, the revised diagnosis changed the treatment plan of all 14 patients who had a pathologic revision (Table 1) and, as such, had a significant impact on their

TABLE 2. Disease Characteristics of Hemato-oncology Medical Tourists and Local Patients Stratified by Hematologic Malignancies, Assuta Medical Centers, Israel, 2014-2016

Characteristic	No./Total No. (%) ^a		Adjusted FDR
	Medical Tourists (n = 110)	Local Patients (n = 122)	
Disease stage III/IV at diagnosis			
Overall study population	44/104 (42.3)	35/115 (30.4)	.062 ^b
NHL	27/59 (45.8)	26/83 (31.3)	.090 ^b
HL	10/36 (27.8)	2/7 (28.6)	.965 ^b
MM (stage III only)	7/9 (77.8)	7/25 (28.0)	.068 ^b
At least 1 treatment cycle was carried out before the first visit			
Overall study population	28/108 (25.9)	13/109 (11.9)	0.048 ^c
NHL	13/58 (22.4)	11/77 (14.3)	0.253 ^c
HL	10/36 (27.8)	0/7 (0)	> 0.999 ^c
MM	5/14 (35.7)	2/25 (8.0)	0.256 ^c
Median follow-up period, days (IQR) [No. of patients]			
Overall study population	110.0 (8.0-303.5) [n = 109]	581.0 (141.0-850.0) [n = 119]	< 0.001 ^c
NHL	112.0 (10.0-335.0) [n = 59]	606.5 (71.5-854.5) [n = 86]	< 0.001 ^c
HL	132.5 (23.2-299.0) [n = 36]	409.0 (6.0-543.0) [n = 77]	0.178 ^c
MM	18.0 (2.5-239.0) [n = 14]	623.0 (359.8-941.7) [n = 25]	0.033 ^c
Complete response to treatment			
Overall study population	35/61 (57.4)	38/97 (39.2)	0.510 ^c
NHL	20/29 (69.0)	27/69 (39.1)	0.655 ^c
HL	15/27 (55.6)	2/5 (40.0)	0.645 ^c
MM	0/5 (0)	9/23 (39.1)	0.192 ^c
B symptoms			
Overall study population	36/77 (46.8)	13/76 (17.1)	< 0.001 ^c
NHL	19/41 (46.3)	10/69 (14.5)	0.001 ^c
HL	17/36 (47.2)	3/7 (42.9)	0.841 ^c
M	NA	NA	NA

Abbreviations: FDR, false discovery rate; HL, Hodgkin lymphoma; IQR, interquartile range; MM, multiple myeloma; NA, not applicable; NHL, non-Hodgkin lymphoma.

^aValues are presented as number/total number and percentage, unless otherwise indicated.

^bAge-adjusted FDR.

^cAge- and disease stage-adjusted FDR.

disease management and outcome. This finding is in accordance with previous reports that approximately 10% of histopathologic diagnoses of patients with lymphoma changed after review.¹² In 9.2% of MTs, the biopsy review changed the original diagnosis, whereas in 16.6% of MTs who did not arrive at AMC with a definitive diagnosis, the review significantly contributed to achieving the correct diagnosis and to the initiation of an appropriate treatment. Furthermore, most of the original unconfirmed diagnoses (6 of 9 diagnoses) were later confirmed as HL. This finding fits the complexity of the hemato-pathologic diagnosis of this disease¹³ and emphasizes the need to perform histologic revisions by experienced hematopathologists using advanced and reliable tools to obtain an unequivocal

diagnosis and determine the appropriate treatment. It should be noted that most hemato-oncology MTs were originally diagnosed in centers with less advanced and experienced pathologic services and, as such, might benefit from appropriate treatment protocols that achieve better outcomes.

MTs choose to seek treatment outside their country of origin, especially in more advanced stages of the disease, for a variety of reasons, including lower costs, shorter waiting times, better medical care, and treatments using more advanced technologies.¹⁴ Our analysis showed that only one third of hemato-oncology MTs chose to undergo a complete diagnosis, treatment, and follow-up process in Israel; another third chose to receive only partial

treatments; and the rest preferred to benefit from the advantages of the Israeli private medical system at the minimum cost (they received a pathologic review and a detailed treatment plan and bought medications, but returned to their home country to undergo the actual treatment). It can be assumed that the two main parameters at stake are the costs and quality of medical treatment. As such, it seems that MTs exercise discretion regarding the financial expenses involved in treating their disease. It appears that undergoing treatment in an Israeli hospital is not perceived by MTs as a mandatory follow-up to their diagnosis, and many rely on their own country's health system for the actual treatment. Interestingly, a significantly higher percentage of noncommitted MTs were diagnosed in their home country, compared with partially committed and fully committed MTs, suggesting that noncommitted MTs have greater trust in their home country's health system. Furthermore, a subanalysis of MTs who received an initial diagnosis in their home country showed that longer duration between initial diagnosis and arrival at AMC is related to more advanced disease stages. Consequently, these results suggest that MTs should receive an optimal treatment plan to make up for this delay.

Regarding the response to treatment, our findings also showed that a similar percentage of MTs and local patients achieved complete response to treatment. Moreover, the finding that fully committed and noncommitted MTs achieved

similar complete response rates suggests that noncommitted patients achieved a good treatment outcome at a lower cost by receiving only a consultation in Israel and going back to their country of origin for treatment.

The main strength of our study is the subgroup analysis of MTs' commitment to treatment in the country of destination. The study's limitations include the lack of clinical information on MTs, such as mortality data or treatment response, particularly in MTs who were not fully committed to the treatment because they continued their follow-up in their home country. Furthermore, our study did not have a sufficient statistical power to enable comparisons between MT subgroups. Finally, the external validity of this study is limited to hemato-oncology MTs who received diagnosis and/or treatment at AMC between 2014 and 2016.

In conclusion, this study showed that MTs often require a pathologic review of their initial diagnosis and are more likely to present with advanced stages of disease. Treating MTs according to the appropriate clinical parameters is expected to yield outcomes similar to those of local patients. As far as we know, this work is the first to describe the clinical characteristics of MTs. Further studies are needed to examine additional diseases and clinical parameters to provide a comprehensive analysis that will enable improving treatment of MTs, while providing quality medical treatment in accordance with accepted current practices.

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Manuscript writing: All authors

Final approval of manuscript: All authors

Accountable for all aspects of the work: All authors

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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No potential conflicts of interest were reported.

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