Ethnic Variation in Toxicity and Outcome of Adjuvant Chemoradiation for Gastric Cancer in Israel

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Abstract. *Background: Data on differences in toxicity and efficacy of chemotherapy and radiotherapy among different ethnic groups is limited. We evaluated differences in toxicity, tolerability and clinical outcome of Ashkenazi and non-Ashkenazi Jews receiving postoperative chemoradiation for locally advanced gastric cancer (LAGC). Patients and Methods: Between 6/2000-12/2007, 84 Ashkenazi patients and 60 non-Ashkenazi patients underwent chemoradiation following resection of LAGC (INT-116 trial). Results: Patients' and tumor characteristics were comparable. Ashkenazi patients experienced significantly higher rates of fatigue, anorexia, and grade 3-4 dysphagia, as well as a trend for a higher rate of diarrhea. The incidence of other toxicities, dose adjustments of chemotherapy and radiotherapy and patient prognosis did not differ. Conclusion: This study shows higher rates of various toxicities among Ashkenazi patients receiving postoperative chemoradiation for LAGC compared to non-Ashkenazi patients. To our knowledge, this is the first study comparing treatment toxicity, tolerability and outcome between these two groups.*

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Ethnic diversity in drug response and toxicity is becoming increasingly recognized as an important factor accounting for inter-individual variation in anticancer drug treatment. Presently, most treatment guidelines for patients with cancer refer to the general population, without taking into account ethnical differences. However, ethnicity-related variations in toxicity and efficacy of different anticancer therapies are being increasingly recognized (1-3). In some countries (*e.g.* Japan), it is common practice to modify Western chemotherapy regimens, based on evidence for higher toxicity in the local population (4-7). Nevertheless, in most of the world, current data regarding this issue are still greatly limited to small retrospective series, and are restricted to populations with relatively distinct ethnic differences, such as the African-Americans or the East Asian populations compared with Caucasians (8). To our knowledge, differences between two groups with subtle ethnic differences, for example two Caucasian communities, have never been reported. In addition there is a need for more data regarding the impact of different toxicity profiles on patient outcome, which may require for dose adjustments.

The Jewish population in Israel can serve as a good model to address this issue, as its population is comprised of different ethnic subgroups living at a similar socioeconomic level. The Israeli Jewish population is composed of two main groups: Ashkenazi Jews and non-Ashkenazi Jews. Ashkenazi Jews are descendants of Jews from central and Eastern Europe. The non-Ashkenazi Jews include oriental Jews and Sephardic Jews, *i.e.* descendants of ancient Spanish and

Portuguese communities which migrated southward to North Africa and eastward to the Balkans, Italy and Turkey (9). Marriage within the community, common in both of these societies in the past, led to a relatively preserved genetic structure and to the accumulation of well-recognized specific inherited disorders (10). The differences between the two main Jewish subgroups are not limited to their genetic background; living for centuries in different areas and cultures, these groups also exhibit various lifestyle dissimilarities (11). Clearly, these two Jewish sub-populations represent two Caucasian ethnic groups with distinct genetic and lifestyle differences, and yet a comparable access to health services, and can therefore help in testing the influence of subtle ethnic differences on toxicity, tolerability and even efficacy of various treatment strategies. There are currently no data on possible differences between the Ashkenazi and non-Ashkenazi Jews in Israel with regard to treatment in any discipline. We therefore conducted this study, using postoperative chemoradiation for locally advanced gastric cancer (LAGC) as a platform to evaluate such differences.

Patients and Methods

Patients. Between 6/2000 and 12/2007, 84 Ashkenazi patients and 60 non-Ashkenazi patients underwent postoperative chemoradiation after R0 (n=120) or R1 (n=24) resection of LAGC. All patients had histologically-confirmed adenocarcinoma of the stomach. Patients had stage IB to IV M0 disease according to the 1997 staging criteria of the American Joint Committee on Cancer (AJCC) (12); an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of ≤2; adequate function of major organs (including cardiac, hepatic and renal functions), an adequate bone marrow function [Hemoglobin >10 g/dl; (WBC) count ≥4000/μl; (PLT) count ≥100,000/μl], and oral caloric intake >1500 kcal per day. All patients underwent chest radiographs and abdomino-pelvic computed tomography (CT) before treatment to exclude distant metastases.

Surgery. The surgical requirement for eligibility was a curative *en-bloc* resection of the tumor. Patients with overt macroscopically involved margins (R2) were excluded. All patients had undergone at least D0 lymph node dissection.

Chemoradiotherapy. The postoperative chemoradiotherapy regimen was given according to the INT-0116 trial (13). The median time from surgery to treatment was 47 days (range 4 to 12 weeks), with one cycle of 5-fluorouracil (5-FU) at 425 mg/m^2/day and leucovorin (LV) at 20 mg/m^2/day, given on days 1-5, and was followed by chemoradiotherapy four weeks after the beginning of this cycle. Chemoradiotherapy consisted of 45 Gy of radiation in fractions of 1.8 Gy/day, five days/week for five weeks, with a reduced dose of 5-FU (400 mg/m^2) plus LV on the first four and the last three days of radiation. Four weeks after radiotherapy completion, two five-day cycles of 5-FU (425 mg/m^2) and LV were given four weeks apart. Radiotherapy was delivered to the tumor bed, as defined by preoperative imaging, the regional lymph nodes, and 2 cm beyond the proximal and distal margins of resection.

Table I. *Patient and tumor characteristics of Ashkenazi and non-Ashkenazi Jews receiving adjuvant chemoradiation.*

Characteristic	Ashkenazi Jews, n(%)	Non-Ashkenazi Jews, n(%)	*p*-Value
Number	84	60	
Age, years			0.178
Median (range)	64 (33-78)	60 (23-86)	
Male/female	54/30 (64/36)	34/26 (57/43)	0.226
Margins status			0.278
R0	69 (82)	51 (85)	
R1	15 (18)	9 (15)	
Grade			0.529
I-II	18 (22)	11 (18)	
III-IV	66 (78)	49 (82)	
Location			0.225
Proximal	29 (35)	12 (20)	
Body	29 (35)	20 (33)	
Distal	25 (29)	26 (44)	
Unknown	1 (1)	2 (3)	
T Stage			0.337
T1-T2	22 (26)	13 (22)	
T3	61 (73)	44 (73)	
T4	1 (1)	3 (5)	
Lymph node status			0.568
N0	15 (18)	10 (17)	
N+	69 (82)	50 (83)	

Patient evaluation. During treatment, patients were evaluated for toxicity before each chemotherapy cycle. Evaluation included physical examination, complete blood count (CBC) and blood chemistry. Hematological and non-hematological toxicities were recorded by grade according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 3 (14) and were compared between the Ashkenazi and non-Ashkenazi patients. Following the completion of adjuvant treatment, patients were followed at 4-month intervals for three years, at 6-month intervals for the next two years and yearly thereafter. Follow-up consisted of physical examination, CBC and liver function tests. Imaging studies and gastroscopy were performed when clinically indicated.

Statistical considerations. Continuous measures were analyzed by ANOVA and parametric by Fisher's exact test or chi-square test; $p<0.05$ was consider as significant. Mortality analysis was based on uni- and multivariate analysis followed by Kaplan–Meier product-limit method. Disease-free survival (DFS) was defined as the time from surgery to the documentation of recurrence of cancer or the last date the patient was known to be recurrence-free for patients with R0 status. Overall survival (OS) was defined as the time from surgery to death or the last date the patient was known to be alive.

Results

Patients. The patient and tumor characteristics of both subgroups comprising the study population, 84 Ashkenazi and 60 non-Ashkenazi patients were similar (Table I). In fact, none of the variables tested was statistically significantly different or even exhibited a trend for any difference between the Ashkenazi and non-Ashkenazi Jews.

Table II. *Hematological toxicity of Ashkenazi and non-Ashkenazi groups after adjuvant chemoradiotherapy.*

	Ashkenazi Jews, n(%)[a]	Non-Ashkenazi Jews, n(%)[a]	*p*-Value
WBC			
Median nadir, $\times 10^3/mm^3$ (range)	3.3 (0.22-10.2)	3.35 (0.2-7.3)	
Any grade	71 (86)	43 (73)	0.491
Grade ≥3	24 (29)	18 (30)	0.312
ANC			
Median nadir, $\times 10^3/mm^3$ (range)	1.7 (0-7.8)	1.65 (0.1-4.5)	
Any grade	51 (61)	34 (58)	0.413
Grade ≥3	28 (34)	18 (31)	0.338
Neutropenic fever[b]	13 (16)	11 (19)	0.402
PLT			
Median nadir, $\times 10^3/mm^3$ (range)	150.5 (11-324)	153.5 (22-344)	
Any grade	29 (35)	19 (33)	0.449
Grade ≥3	3 (4)	1 (2)	0.446

WBC: White blood cells, ANC: absolute neutrophil count, PLT: platelets. [a]Data was missing on WBC (n=2 patients), ANC (n=2), neutropenic fever (n=2), PLT (n=4). [b]Patients with at least one episode of neutropenic fever.

Toxicity. The chemoradiation toxicity was examined by ethnicity. There were no significant differences in hematological toxicity between Ashkenazi and non-Ashkenazi Jews, including the rates of leucopenia, neutropenia anemia, and thrombocytopenia (Table II). However, non-hematological toxicities, mostly gastrointestinal (GI), were more common in Ashkenazi Jews (Table III). Anorexia of all grades occurred in 49% of the Ashkenazi patients and in 30% of the non-Ashkenazi patients (p=0.02). Severe dysphagia was noted in 6% of the Ashkenazi patients and in none of the non-Ashkenazi patients (p=0.036). Diarrhea appeared in 39% of the Ashkenazi and in 25% of the non-Ashkenazi patients, but this finding was just of borderline significance. Constitutional toxicity also differed between the groups, as all-grade fatigue appeared in 58% of the Ashkenazi Jews compared to 32% of the non-Ashkenazi Jews (p=0.001).

Table III. *Non-hematological toxicity of Ashkenazi and non-Ashkenazi groups after adjuvant chemoradiotherapy.*

Toxicity	Ashkenazi Jews, n(%)	Non-askenazi Jews, n(%)	*p*-Value
Diarrhea			
Any grade	33 (39)	15 (25)	0.052
Grade ≥3	8 (10)	5 (8)	0.525
Stomatitis			
All grades	28 (33)	14 (23)	0.132
Grade ≥3	16 (19)	9 (15)	0.485
Nausea			
All grades	55 (65)	37 (62)	0.384
Grade ≥3	4 (5)	6 (10)	0.187
Vomiting			
All grades	32 (38)	28 (47)	0.196
Grade ≥3	4 (5)	5 (8)	0.297
Anorexia			
All grades	41 (49)	18 (30)	0.02
Grade ≥3	1 (1)	1 (1.5)	0.661
Fatigue			
All grades	49 (58)	19 (32)	0.001
Grade ≥3	2 (2)	2 (3)	0.555
Abdominal pain			
All grades	34 (40)	25 (42)	0.511
Grade ≥3	11 (13)	12 (20)	0.555
Dermal			
All grades	3 (4)	6 (10)	0.112
Grade ≥3	0	0	-
Dysphagia			
All grades	19 (23)	11 (18)	0.341
Grade ≥3	6 (7)	0 (0)	0.036

Treatment administration. Considering that augmented toxicity leads to reduced treatment tolerability, it may subsequently affect actual therapy administration. Therefore, we performed a comparison of treatment adjustments for both chemotherapy and radiotherapy between the two groups: 5-FU and LV dose intensities, chemotherapy dose reduction and delays, irradiation delays and completion of chemotherapy and radiotherapy. As seen in Table IV, we did not find any significant differences between the Ashkenazi and non-Ashkenazi patients with respect to any of these parameters.

Patient outcome. The median follow-up was 25.0 months (range=2.6-113.8 months) for all 144 patients. A total of 118 patients had R0 (67 Ashkenazi and 51 non-Ashkenazi) and 23 had R1 resection. Among the R0 patients, 49 (41%) had recurrence of disease: 28 Ashkenazi and 21 non-Ashkenazi. There was no significant difference in the recurrence rate between the Ashkenazi group and the non-Ashkenazi group

Table IV. *Administration of chemoradiation to Ashkenazi and non-Ashkenazi groups.*

	Ashkenazi Jews, n(%)	Non-Ashkenazi Jews, n(%)	*p*-Value
5-Fluorouracil dose intensity	707.5 mg/m^2/week	707.8 mg/m^2/week	0.709
Leucovorin dose intensity	35.7 mg/m^2/week	35.6 mg/m^2/week	0.589
Chemotherapy dose reduction[a]	28 (34)	17 (29)	0.816
Chemotherapy delays[b]	16 (19)	13 (22)	0.78
Irradiation delays[c]	2 (3)	7 (12)	0.269
Completion of chemotherapy[d]	53 (63)	34 (57)	0.272
Completion of radiotherapy[e]	73 (91)	51 (89)	0.473
Completion of chemotherapy and radiotherapy[f]	50 (63)	32 (56)	0.426

[a]At least one chemotherapy cycle with a reduced dose; [b]At least one chemotherapy cycle delayed more than two days; [c]At least one episode of radiotherapy delay of more than three days; [d]All five cycles of chemotherapy given; [e]45 Gy; [f]Five cycles of chemotherapy and 45 Gy.

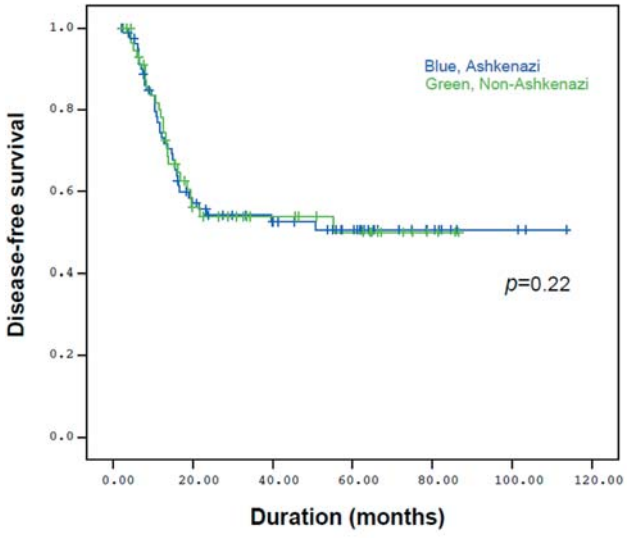

Figure 1. *Disease-free survival of Ashkenazi and non-Ashkenazi Jews undergoing R0 gastrectomy (Kaplan–Meier), followed by chemoradiotherapy.*

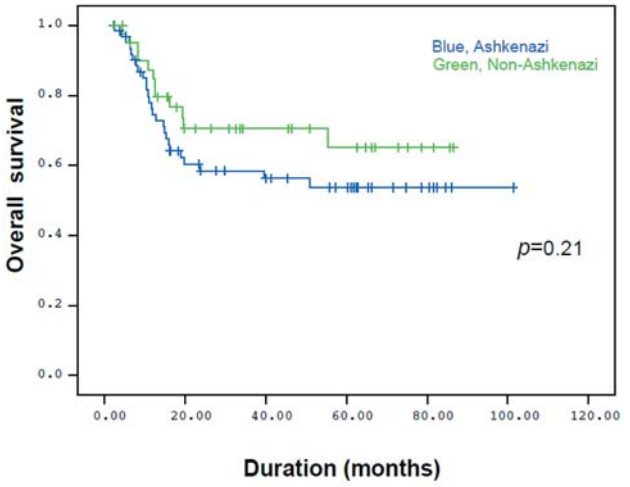

Figure 2. *Overall survival of Ashkenazi and non-Ashkenazi Jews undergoing R0 gastrectomy (Kaplan–Meier), followed by chemoradiotherapy.*

(42% *vs*. 39% respectively; p=0.2). The DFS and OS curves of the R0 group, including both ethnic groups, are shown in Figures 1 and 2, respectively. As seen in these figures, the DFS and OS of the Ashkenazi patients were similar to those of the non-Ashkenazi patients; the 5-year DFS rates of the Ashkenazi and of the non-Ashkenazi patients were 50.6% and 50.0%, respectively (p=0.22) and the corresponding 5-year OS rates were 53.6% and 65.4%, respectively (p=0.21). In a multivariate analysis including age, gender, grade, percentage of patients with signet cell histology, the presence of lymphovascular or perineural invasion, ethnicity did not have an impact on DFS or OS (data not shown).

Discussion

In the current study, we identified ethnical differences in the toxicity of adjuvant chemoradiation therapy in patients who underwent resection of LAGC. During treatment, Ashkenazi Jews experienced higher rates of fatigue, anorexia, diarrhea and dysphagia compared to non-Ashkenazi Jews. However, the need for dose adjustments to chemotherapy or radiotherapy, and the patients' prognoses did not differ between groups.

Earlier studies have demonstrated significant differences in the pharmacokinetics and pharmacodynamics of various drugs between ethnic groups (2). These differences can affect

patient tolerability and thus potentially affect their prognosis. However, in our study patient, outcome was not affected. While our study deals with subpopulations within the Caucasian group (Ashkenazi and non Ashkenazi Jews), most studies to date deal with the main ethnic groups (Caucasians, Asians, Africans etc.). For instance, Axtell *et al*. showed different outcomes between African-Americans and Caucasian Americans with colorectal cancer (15). They and others proposed that changes in toxicity profiles of chemotherapy between these groups may account for the different prognoses (16-18). In another study, McCollum *et al*. showed that among 3,380 patients receiving adjuvant 5-FU for colon cancer, a sub-group of 344 African-Americans had significantly higher hematological toxicity and lower GI toxicity; however, in this case, the prognoses were equal (8). Other studies involving African-Americans demonstrated high rates of cardiotoxicity (all cancer) (19, 20), early termination rates due to neutropenia (breast cancer) (21-24) and increased rates of vincristine-induced neurotoxicity, resulting in dose reductions and treatment interruptions (acute lymphoblastic leukemia) (25).

Differing responses to chemotherapy are also demonstrated among East Asians compared to Caucasians. This issue was addressed in several clinical studies, planned to assess for the optimal dosing of chemotherapy for the Asian population (4-7, 26, 27). In Japan, for example, reduced doses of docetaxel, cisplatin and 5-FU are administered as common practice due to intolerance to standard Western doses (7), mainly due to hematological toxicities such as neutropenia. Similarly, higher rates of toxicity were demonstrated among Singaporean (28) and Chinese (29-31) patients with cancer. Interestingly, at least two studies demonstrated higher response rates and better prognosis among Asian patients receiving epidermal growth factor receptor inhibitors for non-small cell lung cancer (32).

Several biological mechanisms have been proposed to explain the ethnic differences in response to chemotherapy. For example, dihydropiridine dehydrogenase (DPD), the rate-limiting enzyme in 5-FU catabolism, is significantly less active in African-Americans compared to Caucasians (33).

Another example is thymidylate synthetase, the target enzyme of 5-FU. It was proposed that a polymorphism of thymidylate synthetase enhancer region alleles among African-Americans was responsible for different toxicity frequencies of 5-FU (25, 34, 35) . Another example is the higher frequency of somatic *EGFR* mutations in tumors of East Asians, which may account for the better response rates seen in this population when treated with EGFR inhibitors. It has been suggested that these mutations are a result of ethnic germline differences rather than a consequence of an environmental factor (36-38).

The Jewish population of Israel is unique. It is composed of different Jewish subgroups which arrived in the Middle East in the 20th century from various geographical regions. These subgroups were geographically separated and were relatively genetically isolated from the surrounding populations for centuries due to Jewish religious rules. Consequently, different genetic characteristics, including inherited diseases, have accumulated. A group of genetic disorders termed 'Jewish genetic disorders' is a group of Mendelian-inherited disorders which are distinctly prevalent among Ashkenazi Jews, including lysosomal storage diseases such Tay-Sach's syndrome and Gaucher disease, as well as several non-lysosomal storage diseases, such as Bloom syndrome, familial dysotonomia and Fanconi anemia (9, 10). Other diseases with more complex inheritance which are also prevalent in Ashkenazi Jews include inflammatory bowel disease, colorectal cancer and Breast cancer antigen (BRCA)-related breast cancer (11, 39, 40). Oriental and Sephardic Jews (non-Ashkenazi Jews) have different genetic diseases, which are less common in Ashkenazi Jews. These include familial Mediterranean fever, glucose-6-phosphate dehydrogenase deficiency and α- and β- thalassemia (9). Our clinical impression suggested differences in the toxicities between Ashkenazi and non-Ashkenazi patients with cancer in Israel. These accumulating clinical observations, together with the established data of genetic differences between these two populations, created the rationale for this study, which to our knowledge is the first to examine toxicity, tolerability, and outcome between these two groups.

Our findings on toxicity differences between Ashkenazi and non-Ashkenazi Jews are similar to those described by McCollum *et al*. for the American population (8). McCollum described higher constitutional and GI toxicity, with no differences in prognosis, among African-Americans compared to Caucasian Americans treated with chemotherapy for colon cancer.

In general, the common chemotherapy toxicity measures can be divided into objectively-measurable parameters such as hematological or biochemical tests, and subjective measures such as fatigue and anorexia which are based on patient reports. The differences in the toxicity of the Ashkenazi and non-Ashkenazi Jews mainly included subjective parameters (fatigue, anorexia, and dysphagia). While these subjective parameters can be attributed to biological and genetic factors, they might also be attributed to sociological and cultural factors as well. For example, while the nutrition of the Ashkenazi Jews tends to be more Westernized, the nutrition of the non-Ashkenazi Jews tends to be more Mediterranean. In any case, the underlying causes of the differences in toxicities observed in this study are currently unclear.

Conclusion

This study shows a trend towards a higher toxicity among Ashkenazi Jews receiving postoperative chemoradiation for LAGC compared with non-Ashkenazi Jews receiving the

same treatment. The different toxicity profiles were not found to affect the actual administration of treatment, nor patients' outcomes. Further prospective studies, with larger cohorts and different chemotherapy and radiotherapy protocols, can expand our knowledge on the differences in tolerability of these groups, and the possible mechanisms leading to these differences, as well as their practical and prognostic implications.

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