We also reported this overdominant selection, that is, the incidences of cancers in heterozygotes were lower than those in homozygotes in human malignant diseases.\textsuperscript{4,5}

We hypothesized that HLAs might correlate with response to therapy in patients with gastric cancer. To investigate this idea, we selected HLAs as biomarkers for correlation to specific therapies and began analyzing them in cancer patients from January 1977. After decades of data collection, we assessed the correlation between HLA antigens and response to therapies from the perspective of patient outcomes.

Previously, we found correlations between specific patterns of HLA antigens and metastasis and secondary cancer, in addition to the response to therapies after gastrectomies.\textsuperscript{6-9} However, it remains difficult to predict the response to therapy during the decision making process about treatment.

By applying a multivariate analysis method that we developed, we classified Japanese patients into 4 groups\textsuperscript{10} and followed their outcomes. Based on these outcomes for each group, we recommended specific therapies that had proved suitable for a given HLA group.\textsuperscript{11,12}

In this study, under our results, we focused on confirmation whether the specific HLA antigen or haplotype relates to the response to specific therapy, or not.

INTRODUCTION

Human diseases are different, complex, and multifactorial, and even with the same disease, patients can exhibit different disease patterns. With the individual variation among patients in the manifestations of cancer, there is an acknowledged heterogeneity of disease and differences in individual response to drugs; thus, some patients respond to specific therapeutic approaches, and some do not. One possible source of this individual variation may be single nucleotide polymorphisms (SNPs) or mutations. SNPs are abundant in the human genome, and their ultimate effects may be to alter the expected or predicted pharmacokinetics and pharmacodynamics of a drug.

Human leukocyte antigens (HLAs) are glycoproteins present on the surface membranes of nearly every cell in the body. They occur in high concentrations on the surface of white blood cells (i.e., leukocytes) and are the major histocompatibility antigens for tissue recognition. In people, the complex is also called the HLA system and serves as a model of gene polymorphism. MHC molecules are also important components of the immune response.\textsuperscript{1,2} The phenomenon of MHC restriction was first recognized by Doherty and Zinkernagel,\textsuperscript{3} who hypothesized that the great diversity in HLA class I and class II was maintained through exposure to infectious diseases. We also reported this overdominant selection, that is, the incidences of cancers in heterozygotes were lower than those in homozygotes in human malignant diseases.\textsuperscript{4,5}

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ABSTRACT

It is not well known that the correlation between HLA antigens and response to cancer therapy. To evaluate the correlation among patients’ outcome, HLA antigens and therapies, we used the hierarchical clustering analysis (Ward method). We examined HLA antigens as biomarkers as well as models of gene polymorphism in 1753 gastric cancer patients followed over 25 years after treatment. Among these patients, we identified that HLA haplotypes; HLA-B54-Cw1-DQ4-DR4, might be restricting to Fluoropyrimidine drugs plus PSK therapy in gastric cancer. HLA haplotypes including HLA-B54 were candidate predictors for response to FPSK therapy in gastric cancer. HLAs will be useful biomarkers for response to therapy in Japanese patients.

HLA-B54 is a candidate of response to Fluoropyrimidine plus PSK therapy in gastric cancer

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PATIENTS AND METHODS

The patients all had been diagnosed with gastric cancer, and the group had a median age of 60 y (range: HLA-B54 is a candidate of response to FPSK therapy 41 22–93 y) (1245 men, median age 61 y, range: 22–92 y and 508 women, median age 58 y, range: 23–93 y). All patients gave informed consent. A total of 1719 of the 1753 patients had undergone some type of resection.

For peri- and postoperative adjuvant therapy, mitomycin C (MMC; Kyowa Hakko Co., Ltd., Tokyo, Japan) at a dose of 0.4 mg/kg was given intravenously during the operation and at a dose of 0.2 mg/kg on postoperative day 1. In addition, PSK (Krestin, Kureha Chemical Industry Co., Ltd., Tokyo, Japan) at a dose of 3.0 g/day, a nonspecific immunomodulator, and fluoropyrimidine drugs (5-fluorouracil (5-FU; Kyowa Hakko Kogyo Co., Ltd., Tokyo, Japan) at a dose of 150 mg/ day, Futrafur at a dose of 600 mg/day, UFT (Taiho Pharmaceutical Co., Ltd., Tokyo, Japan) at a dose of 300 mg/day), were given orally from within 30 days after treatment and continued until tumor regression. PSK is virtually unrecognized in the US. PSK is a polysaccharide (large molecules made up of chains of linked sugar molecules) complex with immune stimulating effects, and is derived from the edible mushroom Coriolus Versicolor (Fr.) Quel, a member of the Basidiomycetes. It is composed of proteins and polysaccharides and has a molecular mass approximately 100kDa.

All patients without tumor regressions received drug therapy for one year or longer and continued until a satisfactory outcome was achieved.

Blood samples were collected at the Department of Surgery, Tokai University, beginning in Jan 1977, and HLA antigens were examined in the Department of Transplantation Immunology, Tokai University, by using the NIH standard microlymphocytotoxicity method for HLA-A, B, C, DR, and DQ antigens, and throughout Japan at hospitals belonging to the Japanese Society of Strategies for Cancer Research and Therapy from 1987 to Sep 2005. HLA antigens were serologically tested at the Mitsubishi Chemical Medicine Corporation (Tokyo).

We examined HLA antigens as follows; HLA-A; A1, A2, A11, A24, A26, A30, A31, A33, HLA-B; B7, B13, B17, B27, B35, B37, B38, B39, B44,B46, B48, B51, B52, B54, B55, B56, B59, B60, B61, B62, B67, B70, B75, HLA-C; Cw1,Cw3, Cw4, Cw5, Cw6, Cw7, Cw8, HLADR; DR1, DR3, DR4, DR7, DR8, DR9, DR10, DR11, DR12, DR13, DR14, DR15, DR16, and HLA-DQ; DQ2, DQ4, DQ5, DQ6, and DQ7.

The therapies were classified into groups, as follows: without postoperative adjuvant therapy (No adjuvant group, n=607); with PSK (PSK therapy group, n=123); F (F therapy group, n=136); F plus PSK (FPSK therapy group, n=168); MMC (MMC therapy group, n=93); MMC plus F (MF therapy group, n=354); and MMC plus F plus PSK (MFPSK therapy group, n=272).

All statistical analyses were carried out using SPSS software, version 15 (SPSS Inc., Chicago, IL, USA.). Mean values were compared by Student’s-test. The chi-square test was used to compare the prevalence of incidence of HLAs and the prognoses of patients. For evaluate the correlation between HLA haplotype and right patients with possible right therapy, we performed the hierarchical cluster analysis by using Ward method. Results were considered significant when the P value was less than 0.05.

RESULTS

Figure 1 showed the results of the hierarchical cluster analysis by using Ward method in patients who received FPSK. Among them Figure 1a showed the patients who survived over 10 years, while, 1b showed those who were died within 10 years. In patients who survived over 10 years, HLA-B54, -Cw1, -DR4, and -DQ4 antigens were clustered, while in those who were died within 10 years HLA-A2, -Cw1, and -DR4 were clustered, and HLA-B54 and -DQ4 were separated.

In other therapies analyzed, we could not find out the HLA antigens which correlated between death or alive and clustering or not.

Outcomes of the patients with HLA haplotypes including HLA-B54

HLA-B54, -Cw1, -DR4, and -DQ4 positive patients were 261/1753 (14.9%), 550/1753 (31.4%), 648/1753 (37.0%), and 396/1753 (22.6%), respectively. Figures 2 showed the survival curves of patients with HLA-B54 (Fig. 2a), HLA-B54-Cw1 (2b), HLAB54-Cw1-DR4 (2c), HLAB54-Cw1-DQ4 (2d), HLAB54-Cw1-DR4-DQ4 (2e), and HLA-Cw1-DR4-DQ4 (2f). Patients with B54 (7/134), those with B54-Cw1 (12/244), those with B54-Cw1-DR4 (8/172), those with B54-Cw1-DQ4 (7/126), and B54-Cw1-DR4-DQ4 (7/125) who received FPSK therapy were all survived. Patients with HLA-B54 (log rank test, vs. MFPSK, compare to other therapies.

DISCUSSION

We demonstrated the specific HLA antigen as well as haplotypes included HLA-B54 might be a predictor for response to FPSK therapy in gastric cancer.

Unfortunately, at present, there was no data concerning between HLA and response to therapy clinically as well as basically. Unfortunately, these antigens are common in Japanese and Asian countries, not foreign countries. PSK is also familiar to Japanese clinicians and it’s clinical benefit was reported,13 not but foreign countries. As for HLA-B54, significantly increased frequency of HLA-B54 was reported in Japanese patients with diffuse panbronchiolitis, which is considered a Japanese specific disease. These are well coincided in Japan.14,15

We think that HLA system is the best example of polymorphisms for predicting the right patients with response to right therapy at the right time. The ability to assess an individual’s reaction to a drug before prescribing it will increase the physician’s confidence in prescribing and the patient’s confidence in taking the drug.

In conclusion, HLA-B54 is a useful predictor for response to FPSK therapy before treatment, and we think that consideration of HLAs for predictor of response to therapy in the clinical setting is a useful tool.
Figure 1. Dendrograms by using hierarchical cluster analysis in patients who survived over 10 years (1a), while those who were died within 10 years (1b).
Figure 2. Survival curves of patients with HLA-B54 (2a), HLA-B54-Cw1 (2b), HLA-B54-Cw1-DR4 (2c), HLA-B54-Cw1-DQ4, HLAB54-Cw1-DR4-DQ4 (2d), and HLA-Cw1-DR4-DQ4 (2e) according to the actually administered therapy.

No adjuvant therapy actually (--○--), PSK therapy actually administered (---○---), F therapy actually administered (-----○---), FFSK therapy actually administered (-----●---), MMC therapy actually administered (---□---), MF therapy actually administered (-----●---), and MFPSK therapy actually administered (-----▲---).
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