HLA Antigen Status and Outcome of Postoperative Adjuvant Immunochemotherapy in Gastric Cancer ; A Multidimensional Data Analysis

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We investigated whether HLA antigens could act as predictors of the response to therapy in gastric cancer.

The microcytotoxicity assay was used to examine HLA antigens of the A, B, and C loci in 429 patients who underwent gastric cancer resection. HLA antigens were then divided into four categories after quantifying the response pattern. To evaluate the prognostic factors, multivariate analysis using Cox's model was performed in 321 patients using seven variables: sex, age, pTNM stage, postoperative adjuvant therapy, HLA category, and the association of HLA category with the response to postoperative therapy. Patients received either gastrectomy alone, gastrectomy plus chemotherapy, or gastrectomy plus PSK ± chemotherapy. The Cox's analysis indicated that HLA Category 4 patients receiving PSK ± chemotherapy had a better prognosis than those of HLA categories 1, 3, and 4 receiving gastrectomy alone or those of HLA category 1 receiving chemotherapy after gastrectomy.

These results suggest that HLA antigen status can predict the response to therapy and that rational individualized therapy for cancer patients may possibly be designed in the future by evaluating HLA antigens.

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Key words : HLA antigens, gastric cancer, postoperative adjuvant immunochemotherapy, PSK, third quantification method

If it was possible to predict rational or effective forms of individualized therapy for cancer patients before treatment, they should gain both an improved "quality of life" and a better therapeutic outcome. Our strategy of studying the associations between HLA antigens and the effectiveness of postoperative adjuvant therapy is a novel approach to the detection of parameters for making such predictions.

In Japan, gastric cancer appears to be sensitive to chemotherapy¹⁾, but this is not so in the West²⁾. Japanese studies also show a better survival rate for gastric cancer than that found in the West³⁾.

Postoperative adjuvant immunochemotherapy and chemotherapy have been reported to be effective against gastric^{4, 5)} and colon cancer⁶⁾ in Japan and against colon cancer in the USA⁷⁾. Mitomycin C (MMC), fluoropyrimidines, the protein-bound polysaccharide PSK (Krestin), and levamisole have all been used as chemotherapeutic or immunomodulating agents. However, why a response is obtained to postoperative adjuvant therapy have not yet been sufficiently evaluated.

PSK is a nonspecific immunopotentiator that is widely prescribed by the oral route in Japan. It is extracted from *Coriolus vesicolor* (Fr.) Quel, a member of the Basidiomycetes, is composed of both proteins and

polysaccharides, and has a molecular weight of approximately 100,000. An antitumor activity of PSK has been demonstrated in experimental animal models^{8, 9)}, and a beneficial therapeutic effect has been noted in clinical studies of esophageal¹⁰⁾, gastric, and colon cancer.

In this study, we classified the subjects according to the theory of quantification of response^{11, 13)}. Then we retrospectively studied the association between the HLA antigen status of gastric cancer patient, and the effect of postoperative adjuvant therapy on survival.

Materials and methods

From June 1979 to June 1990, HLA antigens of the A, B, and C loci were examined preoperatively in 429 patients with histologically confirmed adenocarcinoma of the stomach using the standard lymphocyte microcytotoxicity assay¹²⁾. Their ages ranged from 22 to 93 years (median: 57.6 years), and 67.4% were men. Tissue typing was performed for the following antigens: A loci-1, 2, 3, 9, 10, 11, w19, 24, 26, 31, w33; B loci-5, 7, 12, 13, 15, 16, 17, w22, 27, 35, 37, 39, 40, 44, w46, w48, 51, w52, w54, w55, w56, w59, w60, w61, w62, w67; and C loci-w1, w3, w4, and w7.

To explore relationships among the HLA antigens, a factor analysis method was applied. Patients were categorized based on the theory of quantification of the response pattern (third quantification method¹³⁾), which is equivalent to the correspondence analysis method of

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Table 1 Clinical profile of the different treatment groups

	GA	CT	PSK	Total
Sex				
Female	22	36	43	101
Male	68	62	90	220
Age				
<49	21	35	33	89
50-59	21	25	44	90
60-69	24	21	33	78
70+	24	17	23	64
Stage				
1A	71	16	67	154
1B	10	12	17	39
2	3	18	17	38
3A	0	15	10	25
3B	0	5	6	11
4	6	32	16	54
Category				
I	13	17	21	51
II	10	12	20	42
III	43	41	52	136
IV	24	28	40	92

PSK : gastrectomy + PSK ± chemotherapy

CT : gastrectomy + chemotherapy

GA : gastrectomy

Benzeri¹⁴). Multivariate analysis using Cox's model was performed with seven variables : sex, age, pTNM stage, postoperative therapy, HLA category, and the association of HLA category with the response to postoperative therapies. Of the 429 gastric cancer patients, 321 received either gastrectomy, gastrectomy with chemotherapy, or gastrectomy with PSK ± chemotherapy, while 108 received gastrectomy plus treatment with various other chemotherapeutic or immunomodulating agents. A total of 321 patients were evaluated for prognosis by multivariate analysis. The treatment plan and the use of chemotherapy were left up to the judgment of the attending doctors. A clinical profile of the 321 patients is shown in Table 1.

Ninety patients received only gastrectomy, 98 had gastrectomy plus chemotherapy, and 133 had gastrectomy plus PSK (Kureha Chemical Industry Co. Ltd., Tokyo, Japan) ± chemotherapy. Postoperative adjuvant chemotherapy was started with then intravenous administration of mitomycin C (MMC) (Kyowa Hakko Kogyo Co. Ltd., Tokyo, Japan) (20 mg intraoperatively and 10 mg on postoperative day 1). This was followed on postoperative day 14 with the oral administration of fluoropyrimidines, such as N1-(2'-tetrahydrofuryl)-5-fluorouracil (Futrafal) (Taiho Pharmaceutical Co Ltd., Tokyo, Japan) at 600 mg/day or 5-fluorouracil (5-FU) (Kyowa Hakko Kogyo Co Ltd, Tokyo, Japan) at 150 mg/day. Of these 98 patients, 19 received MMC alone, 14 received fluoropyrimidines alone, and 65 received MMC plus fluoropyrimidines.

Fig.1 The four categories of HLA antigens

Sixty-five patients received PSK (3.0 g/day) alone starting on POD 14 after gastrectomy, and 68 received postoperative adjuvant chemotherapy plus PSK. The chemotherapy given with PSK was as follows : 2 patients received MMC alone, 14 received fluoropyrimidines alone, and 52 received MMC plus fluoropyrimidines. Fluoropyrimidines or PSK were administered orally over a period of 3 months.

All resected tumor specimens were subjected to detailed pathological examination, and the patients were then staged according to the 1987 pTNM staging of the UICC.

Survival was assessed from the day of surgery until death. Follow-up information was obtained by outpatient appointment or telephone contact with the patients themselves or their families. The 2-, 3-, 5-, and 10-year follow-up rates were 100.0%, 66.0%, 42.7% and 33.3%, respectively. Statistical analysis was carried out using the SAS software.

Results

Seven HLA antigens could not be evaluated : the sample size was too small for A-1, A-26, B-17, B-27, B-37 and B-67, while A-24 was not evaluated because of it corresponds to A-9. The remaining 34 HLA antigens were classified into the following four categories using the quantification of response pattern : Category I (A-3, Aw-19, Aw-33, B-12, B-44, Bw-56, B-35), category II (Aw-31, B-5, B-51, B-13, Cw-4), category III (A-2, A-9, Bw-52, B-7, B-15, Bw-62, B-16, B-39, B-40, Bw-60, Bw-48, Cw-7), and category IV (A-10, A-11, Bw-22, Bw-54, Bw-55, Bw-61, Bw-46, Bw-59, Cw-1, Cw-3) (Fig.1).

Table 2 Univariate analysis in 321 gastric cancer patients

Variable	Parameter estimate	Chi-squared test	p value	Risk ratio
Sex				
Female	0			1
Male	0.062949	0.05836	NS	1.065
Age				
-49	0			1
50-59	0.502040	1.89398	NS	1.652
60-69	0.954591	5.95895	0.0146	2.598
70-	1.441960	16.24727	>0.0001	4.229
Stage				
1A	0			1
1B	0.831285	2.30323	NS	2.296
2	1.455448	8.68176	0.0032	4.286
3A	2.149307	16.72218	>0.0001	8.579
3B	2.662640	13.56041	0.0002	14.334
4	4.166280	88.80954	>0.0001	64.475
Therapy				
PSK	0			1
CT	0.316713	1.23694	NS	1.373
GA	1.146060	9.23476	0.0024	3.146
Category				
III	0			1
IV	0.476069	2.90970	NS	1.610
II	0.488028	1.49277	NS	1.629
I	0.972067	8.68125	0.0032	2.643

NS : P>0.05

PSK : gastrectomy + PSK $\pm$ chemotherapy

CT : gastrectomy + chemotherapy

GA : gastrectomy

Table 2 shows the results of univariate analysis of maximum likelihood estimates. Patients treated with PSK $\pm$ chemotherapy after gastrectomy showed a significantly better outcome than those receiving gastrectomy alone. In addition, patients in HLA category III showed a significantly better outcome than those in HLA category I.

Table 3 shows the results of multivariate analysis of the factors influencing the survival of patients after gastrectomy alone, gastrectomy plus chemotherapy, or gastrectomy plus PSK $\pm$ chemotherapy. The gastrectomy plus PSK $\pm$ chemotherapy patients in HLA category IV showed significantly better results than gastrectomy patients of HLA categories I, III and IV or gastrectomy plus chemotherapy patients of category I.

Discussion

Evaluation of parameters that are correlated with the response to treatment would allow the more rational or suitable use of cancer therapy.

For example, we have previously found that gastric cancer patients with abnormal pretreatment sialic acid levels showed a better response when they were given PSK in combination with chemotherapy¹⁵⁾, while

Table 3 Multiple variate analysis by Cox's model in 321 gastric cancer patients

Variable	Parameter Estimate	Chi-squared test	p value	Risk ratio
Sex				
Female	0			1
Male	0.028669	0.01163	NS	1.029
Age				
-49	0			1
50-59	0.476537	1.67428	NS	1.610
60-69	0.919181	5.48559	0.0192	2.507
70-	1.472195	16.44272	>0.0001	4.359
Stage				
1A	0			1
1B	0.891210	2.59558	NS	2.438
2	1.452635	8.26260	0.0040	4.274
3A	2.217470	17.15558	>0.0001	9.184
3B	2.594512	12.26014	0.0005	13.390
4	4.129570	86.17772	>0.0001	62.151
Therapy & Category				
IV & PSK	0			1
III & PSK	0.103809	0.02951	NS	1.109
III & CT	0.159352	0.08222	NS	1.173
II & CT	0.545904	0.62807	NS	1.726
II & PSK	0.750140	1.15924	NS	2.117
IV & CT	0.978159	3.19342	NS	2.660
I & PSK	1.024997	2.41072	NS	2.787
III & GA	1.185294	4.01960	0.0450	3.272
I & CT	1.206693	4.23839	0.0395	3.342
II & GA	1.432099	1.55132	NS	4.187
IV & GA	1.433725	4.13607	0.0420	4.194
I & GA	2.005852	6.25254	0.0124	7.432

NS : P > 0.05

PSK : gastrectomy + PSK $\pm$ chemotherapy

CT : gastrectomy + chemotherapy

GA : gastrectomy

patients with abnormal levels of immunosuppressive acidic protein showed a better response, when they were given PSK in combination with chemotherapy after total gastrectomy and splenectomy than those with normal levels¹⁶⁾. Therefore, it seems that the levels of acute phase reactants such as sialic acid and immunosuppressive acidic protein may predict the effectiveness of immunotherapy using PSK.

However, such predictors do not allow us to select individualized therapy for a single patient, i.e., we cannot assure each cancer patient that the therapy being offered is rational and will achieve a good result. Because each individual has a unique HLA type, we selected HLA antigen status for investigation in the present study.

PSK may induce its antitumor effect by promoting interferon and interleukin-2 production^{17,18)}. PSK is also considered to be a potent inducer of gene expression for some interleukins (interleukin-1 α , - β , -6, -8), tumor necrosis factor- α , and monocyte chemotactic and activating factor¹⁹⁾. Thus, the antitumor activity of PSK

probably depends on its regulation of host immunity and its ability to normalize the immunosuppressed state of cancer patients.

Chemotherapy such as adriamycin, MMC and fluoropyrimidines may induce cell-mediated cytotoxicity^{20, 21)} and may also promote the production of cytokines such as interleukin, and ρ -interferon^{22, 23)}. Experimental studies have also indicated that the HLA phenotype can influence the immune response²⁴⁾. This may explain why certain HLA antigens appear to correlate with various chemotherapy regimens. Thus, chemotherapy agents as well as immunomodulating agents may influence the host immune response. HLA antigens can be seen as a useful marker for both the immune response and for identification of the characteristics of an individual patient.

It has also been reported that in cell lines negative for HLA-DR expression, HLA-DR synthesis and expression can be induced by ρ -interferon²⁵⁾. In addition, tumor cells in biopsy specimens from ρ -interferon nonresponders were found to be negative for the expression of DR antigens both before and after treatment. Furthermore, it has been suggested that the HLA-DR antigens expression by tumor cells may play a role in the response to interleukin-2 with or without lymphokine-activated killer cells, and that marked tumor infiltration by T cells accompanies and possibly mediates such a response²⁶⁾. A recent study demonstrated that major histocompatibility complex (MHC) class I-positive tumors stimulated autologous lymphocytes more frequently than did class I-negative tumors²⁷⁾. In addition, the HLA B locus is adjacent to that for tumor necrosis factor^{28, 29)}. All these observations suggest that there may be an association between HLA phenotype and the effectiveness of anticancer therapy, especially immunotherapy.

An association between HLA antigens and survival has been reported for gastric cancer, and the expression of HLA DR4 and HLA-DR by tumors is apparently associated with a good prognosis^{30, 31)}.

There have only been a few reports concerning associations between HLA antigens and the effectiveness of anticancer therapy. An association between HLA antigens and the response to immunotherapy was reported by Tursz et al.³²⁾. They found that long-term survivors of lymphoblastic leukemia who received BCG immunotherapy had a high frequency of HLA Aw33 or B17 compared with healthy controls, but the actual HLA phenotype responding to immunotherapy was not clarified. We have previously reported that gastric cancer patients with HLA-Bw40 antigen showed a good response to PSK combined with chemotherapy³³⁾.

Regarding the association between the response to PSK and MHC antigens, Vanky et al. reported that in the presence of PSK, tumor cells with low-class-I-antigen-expression could undergo lysis by lymphocytes, and suggested that PSK potentiated the function of antigen-specific lymphocytes but did not generate such cells³⁴⁾.

We used the quantification of response method to classify HLA antigens associated with a similar response to therapy. This method has usually been utilized for classification of data, e.g. in surveys of national characteristics^{35, 36)}, and is one method of classifying individuals on the basis of similarity of responses to categorical questions. Using this method, the configurations of both the individuals and the categories in a multidimensional Euclidian space is able to provide inferences regarding their categorization.

Using this method, we categorized HLA antigens into four groups and then found that the therapeutic results of gastric cancer patients in different categories had different responses to the various adjuvant therapies.

From the published literature and our results we speculate that the level of MHC expression by lymphocytes is correlated with the response to therapy and that there may be restriction among HLA antigens, T cell receptors, and the PSK receptor. However, we do not have a definite mechanism to propose as yet.

It appears that HLA antigen status should be considered when we treat patients with anticancer therapy. Our findings also emphasize that it is important to consider a patient's genetic constitution when managing malignant disease. It is of obvious benefit to individual patients if we can select those who are likely to respond before initiating therapy. Moreover, HLA typing may lead to clues on the genetic origin of tumor resistance to immunotherapy and chemotherapy, as well as information on how certain types of drug resistance may be prevented or overcome and on the development of more rational and effective treatment protocols. Thus, the approach of individualizing cancer therapy by HLA typing of patients holds some promise for the future.

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HLA Antigens and Postoperative Adjuvant Immunotherapy in Gastric Cancer ; a Multidimensional Data Analysis

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癌治療を行う前に、効果のある、患者個人個人に最適な治療法の予測が可能であれば、癌患者のquality of life (QOL) の向上に役立つものと考えられる。そこで、本研究では、個人を同定出来るHLA抗原を用いて、個人個人の治療法が予測できないかどうか検討を行った。

【対象と方法】 対象患者の術前にmicrocytotoxicity assayを用いてHLA-A, -B, -C抗原を測定した。HLA抗原の分類は、胃癌切除例429例を対象とし、数量化Ⅲ類^{11, 12)}を用いて四つの型に分類した。予後因子の検討は、胃切除術単独90例、胃切除術+化学療法98例、胃切除術+PSK併用免疫化学療法133例を対象として、Coxの比例ハザードモデルを用いて解析した。

【結 果】 ① 数量化Ⅲ類により、1型はA-3, Aw-19, Aw-33, B-12, B-44, Bw-56, B-35抗原、2型はAw-31, B-5, B-51, B-13, Cw-4抗原、3型はA-2, A-9, Bw-52, B-7, B-15, Bw-62, B-16, B-39, B-40, Bw-60, Bw-48, Cw-7抗原、4型はA-10, A-11, Bw-22, Bw-54, Bw-55, Bw-61, Bw-46, Bw-59, Cw-1, Cw-3抗原に分類された(図1)。

② 単一予後因子としての年齢は49歳以下の患者が最も予後良好で、60歳以上の患者との間、進行度では、pTNM stage 1Aの患者がもっとも予後良好で、stage 2, 3A, 3B, 4の患者との間、治療法別では、PSK併用免疫化学療法群がもっとも予後良好で、胃切除群との間、HLA分類型は、3型が最も予後良好で、1型との間に有意差を認めた(表2)。

③ 多因子での検討では、HLA抗原型4型でPSK併用免疫化学療法施行群が最も予後良好で、1型、2型、3型の胃切除群、1型の化学療法施行群に比し有意に予後良好であった(表3)。

【考 察】 われわれは、術前のシアル酸が異常値を示す症例、または血清IAP (immunosuppressive acidic protein) 値が異常値を示し、脾臓摘出がなされた症例では、術後PSK併用免疫化学療法が最適な治療法であることを報告した^{14, 15)}。一方、個人を同定出来るHLA抗原を用いて検討を行ったところ、HLA-Bw-40抗原陽性胃癌患者のPSK併用免疫化学療法施行例は予後良好であった³²⁾。しかし、HLA抗原はその特徴として多様性を示すことが知られている。そこで、本研究では、数量化Ⅲ類を用いてHLA抗原の発現頻度からHLA抗原を群として分類し、治療法と予後を検討したところ、HLA抗原のパターンと治療法により予後が異なっていた。このことはHLA抗原のパターン(そのようなHLA抗原を持っている患者)に相対する最適な治療法が存在することを示しているものと考えられる。よって、癌患者のHLA抗原の測定は、個人個人の最適な治療法の予測に有用であると考えられた。

Investigation of Thymidylate Synthase Induction in Colorectal Tissues after Administration of Anticancer Drug, Fluorinated Pyrimidine Fluoride Derivatives

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Kitaro Futami et al.

大腸癌に対してUFTならびにTegafurの術前投与を行い、組織内5Fu濃度およびTS阻害率を比較検討するとともに、薬剤非投与例をコントロールとして、抗癌剤投与による組織内TSの変動についても検討を加えた。

【対象と方法】 大腸癌切除症例48例を対象とした。37例は薬剤投与例(UFT投与群20例、Tegafur投与群17例)であり、術前7日間おのおの600mg、分3とし経口連続投与を行った。手術時、腫瘍組織、正常部粘膜、リンパ節(1群領域)を採取し、凍結保存ののち各組織における5Fu濃度、TS量、TS阻害率を測定し、UFT群とTegafur群を比較した。また、11例の薬剤非投与例についても各組織のTS量を測定し、薬剤投与群と比較した。

【結 果】 薬剤投与群における5Fu濃度の比較では腫瘍組織においてUFT群がTegafur群に比し、有意に高値であった。また、TS阻害率についてもUFT群で有意に高い阻害率を示した。各組織におけるTS量については、UFT群、Tegafur群とも薬剤非投与群に比較し、有意に高いTS量を示し、UFT群でより顕著であった。腫瘍組織におけるTS量とTS阻害率の関係をみると、TS量に関係なく、TS阻害率は50~60%の値であった。

【考 察】 術前1週間連続投による組織内5Fu濃度およびTS阻害率の検討を行い、腫瘍組織においてUFT群でTegafur群に比し有意に高い値を示し、大腸癌に対してもUFTがより強い抗腫瘍効果を期待しうる因子を備えていると考えられた。抗癌剤による組織内TSの変動については、腫瘍組織において非投与群にくらべUFT群で3.3倍、Tegafur群で2.4倍、正常粘膜でもおのおの3.2倍、2.3倍のTS誘導が生じていた。しかしながら、TS量に関係なくTS阻害率は50~60%に留まっていた。この程度の値が臨床投与量におけるUFT単独投与の限界とも考えられる。

最近の知見にて、5FuとCDDPあるいはLeucovorin併用効果のメカニズムが解明されている。5FuのDNA合成障害に最も重要となるFdUMP-TS-met-hylen hydrofolate (Me-THF) のternary complex形成の上で不足したMe-THFがCDDP代謝過程で補れることにより、ternary complex形成が促進され相乗効果を発揮することが証明されている。今回のTS量が増えても、阻害率に反映しないという結果もその原因をMe-THF枯渇に求めることもできるが、今後TSだけでなく、Me-THFの検索が必要であろう。

大腸癌は胃癌にくらべ、TSにより強く依存し、TS阻害により感受性が高いとも考えられており、薬剤側因子からみて大腸癌に対してもTegafurにくらべTSの誘導が強いUFTの効果が期待されるところである。