Polymorphisms in hMSH2 and hMLH1 and response to platinum-based chemotherapy in advanced non-small-cell lung cancer patients

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Platinum-based chemotherapeutics are the most common regimens for advanced non-small-cell lung cancer (NSCLC) patients. However, it is difficult to identify platinum resistance in clinical treatment. Genetic factors are thought to represent important determinants of drug efficacy. In this study, we investigated whether single-nucleotide polymorphisms (SNPs) in human mutS homolog 2 (hMSH2) and the human mutL homolog 1 (hMLH1) were associated with the tumor response in advanced NSCLC patients received platinum-based chemotherapy in Chinese population. Totally, 96 patients with advanced NSCLC were routinely treated with cisplatin- or carboplatin-based chemotherapy. The three-dimensional (3D), polyacrylamide gel-based DNA microarray method was used to evaluate the genotypes of hMSH2 gIVS12-6T/C and hMLH1-1151T/A with peripheral lymphocytes. We found that there was a significantly increased chance of treatment response to platinum-based chemotherapy with the hMSH2 gIVS12-6T/C polymorphism. The 3D polyacrylamide gel-based DNA microarray method is accurate, high-throughput, and inexpensive, especially suitable for a large scale of SNP genotyping in population.

Keywords single-nucleotide polymorphism (SNP); gene-chip/microarray; non-small-cell lung cancer (NSCLC); chemotherapy

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Introduction

Lung cancer, predominantly non-small-cell lung cancer (NSCLC), is one of the leading causes for cancer-related deaths, which was expected to account for almost 30% of all female cancer deaths in the USA in 2007 [1]. Furthermore, after potentially curatively treated, 5-year survival rates for patients with early-stage NSCLC remained only 40% [2]. Recently, NSCLC has become the most fatal cancer in cities in China.

Chemotherapy based on the platinum regimens such as cisplatin or carboplatin is the backbone treatment for advanced NSCLC, and it has been shown to improve the overall survival (OS) rate [3]. However, patients in the same stage usually display the unequal response or varied prognoses. In lung cancer, individual chemotherapy based on pharmacogenetics and pharmacogenomics has demonstrated a potentially predictive or prognostic role to reach the preferable outcome in retrospective studies [4,5]. The identification of the mechanisms that confer sensitivity to these chemotherapeutic agents to avoid toxicity among each individual patient is appealing.

Platinum compounds form the platinum-DNA adducts when they bind to DNA, which were thought to be the major mechanism for the cytotoxicity of the drug [6,7]. Because DNA repair enzymes were proved to be closely associated with DNA damage induced by anticancer agents, it was hypothesized that single-nucleotide polymorphisms (SNPs) in DNA repair genes might influence the treatment outcome.

DNA mismatch repair (MMR) system, one of the DNA repair systems, mainly includes the hMutS complex (composed of MSH2, MSH6, and MSH3) and the hMutLa complex [human mutL homolog 1 (hMLH1) and PMS2]. The MMR plays a critical role in correcting replicative errors, repairing DNA mismatch lesions, and maintaining the integrity of the genome [8]. In the processing of antitumor agents such as cisplatin, human mutS homolog 2 (hMSH2) and hMLH1 were involved directly in...
recognizing GpG intrastrand adducts of cisplatin, almost without function of repairing cisplatin adducts [9–12]. Interestingly, although at least 10 proteins are related to MMR, the DNA MMR system is most enormously affected by the abnormal MSH2 or MLH1 function [9,13]. And it was clinically significant that the down-regulation or mutations in MMR genes, hMLH1 or hMSH2, were observed consistently in cisplatin resistance, the level of which induced by the loss in MMR was ~2–5 folds [14–17]. Therefore, there was a hypothesis that the functional polymorphisms in the MMR genes might be associated with response to platinum-based chemotherapy in NSCLC.

In the present research, we focused on gene polymorphisms in hMSH2 gIVS12-6T/C and hMLH1-1151T/A. Polymorphism in hMSH2 gIVS12-6 has a T to C substitution at the position-6 intronic splice acceptor site of exon 13 and was shown to be related to non-Hodgkin lymphoma, sporadic and familial colorectal cancer, ulcerative colitis cancer, and acute myeloid leukemia [18–22]. It is noteworthy that Jung et al. [23] reported that the presence of at least one hMSH2 gIVS12-6C allele was associated with a significantly increased risk of lung adenocarcinoma compared with the homozygous gIVS12-6T wild-type. The hMLH1, one of important MMR genes, was located in the 3p21.3-22 region. An SNP in the hMLH1 gene, involving a T to A substitution designed as hMLH1-1151, results in a valine (Val) to aspartate (Asp) amino acid change at codon 384.

hMLH1 and hMSH2 encode DNA MMR enzymes and both genes are thought to play the most important roles in DNA MMR. However, no study on the relation between DNA mismatch pathways and clinical response to cisplatin in NSCLC has been reported. To test the ability of predictive response to chemotherapy in NSCLC patients, we prospectively assessed the status of the DNA MMR polymorphisms in hMLH1-1151T/A and hMSH2 gIVS12-6T/C and investigated whether these two SNPs can predict the response to cisplatin-based regimens in advanced NSCLC patients in the Chinese population.

Materials and Methods

Patient selection and treatment
Totally, 165 patients with histologically confirmed NSCLC were recruited prospectively from March 2006 to September 2007. All patients were mainly from three hospitals, 98 of 165 from Jiangsu Cancer Hospital, 35 from Zhongda Hospital, and 32 from the Nanjing General Hospital of Nanjing Military Command. The staging of all patients is according to the AJCC Cancer Staging Handbook [24]. To avoid the confounding effect of differences in outcome resulting from clinical stage, only stage III and IV patients were included in the analysis. Given that SNPs evaluated in the present study are potentially relevant to therapies based on platinum, only the response to the first cisplatin/carboplatin-based regimen was evaluated. Patients who had received previous chemotherapy were excluded. Finally, there were 96 patients who were appropriate in this study. The enrolled 96 patients received only chemotherapy and did not receive radiation. These patients were 34–79 years old, and the median was 58 years old, and their main characteristics are shown in Table 1.

On entry into the study, each of the patients had a personal interview including age, sex, native place, smoking status, and family history of cancer. Blood samples (5 ml) were collected from each patient and frozen (−80°C) until the assay was performed. Information about cancer clinical stage, treatment, and the side effect were obtained from the patients’ medical records. All patients agreed to perform genotype analyses in this study and the ethics committees of participating institutions approved this protocol.

Chemotherapy regimens and clinical response evaluation
All patients had received platinum-based chemotherapy; 3 received NP/NC (DDP/CBP plus vinorelbine), 51 had GP/GC regimens (DDP/CBP plus gemcitabine), and 42 were given TP/TC regimens (DDP/CBP plus taxol/docetaxel) (Table 1). Concrete dosage: DDP 30 mg/m² on Days 2–4; CBP AUC 4–5 g on Day 1; vinorelbine 25 mg/m² on Days 1 and 8; gemcitabine 1 g/m² on Days 1 and 8; docetaxel 60 mg/m² on Day 1 (kept for 3 h); docetaxel 60 mg/m² on Day 1 (kept for 1 h). All chemotherapeutic drugs were administered intravenously, and treatment cycles were repeated every 3–4 weeks. Patient responses to treatment were determined after four cycles by the WHO criteria [25], which classified the response into four categories:

### Table 1 Patient clinic pathologic characteristics and chemotherapy regimens

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Patients [n (%)]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>32 (33.3)</td>
</tr>
<tr>
<td>Male</td>
<td>64 (66.7)</td>
</tr>
<tr>
<td>History</td>
<td></td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td>23 (24.0)</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>70 (72.9)</td>
</tr>
<tr>
<td>Large cell and undifferentiated carcinoma</td>
<td>3 (3.1)</td>
</tr>
<tr>
<td>Chemotherapy regimens</td>
<td></td>
</tr>
<tr>
<td>DDP/CBP + TAX/TXT/DOC</td>
<td>42 (43.8)</td>
</tr>
<tr>
<td>DDP/CBP + GEM</td>
<td>51 (53.1)</td>
</tr>
<tr>
<td>DDP/CBP + NVB</td>
<td>3 (3.1)</td>
</tr>
<tr>
<td>DDP, cisplatin; CBP, carboplatin; TAX, taxol/paclitaxel; TXT, taxetere; DOC, docetaxel; GEM, gemcitabine; NVB, vinorelbine.</td>
<td></td>
</tr>
</tbody>
</table>

SNPs evaluated in the present study are potentially relevant to therapies based on platinum, only the response to the first cisplatin/carboplatin-based regimen was evaluated. Patients who had received previous chemotherapy were excluded. Finally, there were 96 patients who were appropriate in this study. The enrolled 96 patients received only chemotherapy and did not receive radiation. These patients were 34–79 years old, and the median was 58 years old, and their main characteristics are shown in Table 1.

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complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD). In the case of CR (disappearance of the disease) and PR (at least 50% reduction in tumor load of the lesions), we considered these patients as good responders. Patients with SD (≤25% progression or <50% shrinkage) or PD (size enlargement >25% or appearance of new lesions) were classified as poor responders.

DNA extraction and SNP genotyping
Genomic DNA was obtained from peripheral blood using QIAamp DNA blood mini kit (Qiagen, Shanghai, China). The genotyping procedure involved polymerase chain reaction (PCR) and the three-dimensional (3D) polyacrylamide gel-based DNA microarray method [26]. This method was developed by researchers in the State Key Laboratory of Bioelectronics, Southeast University in 2005 (Patent code: 200510040597.3 and 200510041508.7).

Probes and primers were designed by Primer Premier 5.0 software. One of each pair primers was modified with acrylamide phosphoramidite (Acrydite™; Matrix Technologies, Hudson, USA) at its 5'-terminal. Each couple of probes was labeled with Cy3 and Cy5 fluorescent dyes at 5'-terminal, respectively (Table 2). The PCRs were performed in the 30-μl reaction solution containing 10 pmol primer and 50 ng genomic DNA. The PCR consisted of an initial step at 95°C for 5 min, then 35 cycles of denaturing at 94°C for 30 s, annealing at 60°C for 30 s, and extending at 72°C for 40 s and a last extension at 72°C for 5 min.

After PCR amplification and gel electrophoresis test, PCR products were processed by ethanol precipitation, evaporation, or left untreated. Solutions containing acrylamide-modified PCR products, glycerol, ammonium persulfate, and acrylamide monomers were prepared, spotted, and polymerized onto the acryl-modified slide. In the process, tetramethylethylene diamine was introduced onto the spotted microarray to immobilize the modified nucleic acids [26]. Following the attachment, to obtain ssDNA for hybridization analysis, dsDNA on the slides was denatured in 0.1 M NaOH for 10 min. After hybridization, the slide was subjected to electrophoresis under 5–30 V/cm for 5–20 min in 1 × Tris-borate-ethylene diamine tetraacetic acid buffer at 4°C. Images of the slides were captured by a scanner (LuxScan™-10K Confocal Scanner, Packard Bioscience Company, Downers Grove, USA) and were analyzed with Genepix Pro 3.0 software.

Statistical analysis
Deviations from the Hardy–Weinberg equilibrium for each SNP genotype were assessed using the Pearson $\chi^2$ test. The association between each polymorphism was tested using Fisher’s exact test. Demographic and clinical information was compared across genotype, using the Pearson $\chi^2$ test. The significance of differences in genotypes between good and poor responders was calculated using the Pearson $\chi^2$ test. Logistic regression was used to analyze the relative risk of responding to treatment with a 95% confidence interval (CI). Statistical analysis was performed using SPSS software package version 13.0 (SPSS Inc., Chicago, USA).

Results
Patient and treatment characteristics
Patient characteristics are listed in Table 1. The median age was 58 years (from 34 to 79 years) and 33.3% of the patients were female. All patients received a platinum agent in addition to each other chemotherapy drug including Gemcitabine (53.1% of the total number of patients), taxane (43.8%), or vinca alkaloid (3.1%).

Images of DNA microarray for SNP genotyping
Images of the gene polymorphisms are presented in Fig. 1. Sequencing of 10% samples randomly selected was performed to validate the results from the 3D polyacrylamide
gel-based DNA microarray method. The concurrence rate of these two methods was 100%, suggesting that the 3D polyacrylamide gel-based DNA microarray method is reliable.

Allele frequencies
The genotypic frequencies for each polymorphism are presented in Table 3. Two stages of genotype frequencies for both HMLH1-1151 and hMSH2 gIVS12-6 polymorphisms were found to be in the Hardy–Weinberg equilibrium. No associations were detected between genotype and age, sex, or histological type.

Gene polymorphisms and clinical response
Four out of 28 cases with good response were homozygosis for hMSH2 compared with 1 of the 68 cases with poor response, and logistic regression analysis showed a significantly increased chance of treatment response with the C/C genotype vs. the T/T genotype (odds ratio 0.275; 95% CI: 0.1391–0.5436; \(P = 0.0166\); Table 4); after adjusting for patient gender, age at diagnosis, tumor histology, disease stage, and chemotherapy regimens, the OR for response were 0.046, and the 95% CI were between 0.004 and 0.580 \(P = 0.0173\). For the hMLH1-1151T/A locus, however, the genotypes were not substantially different between the groups.

### Table 3 Allele frequencies of the indicated gene variants

<table>
<thead>
<tr>
<th>Gene variant</th>
<th>Wild type ([n (%)])</th>
<th>Heterozygous* ([n (%)])</th>
<th>Homozygous* ([n (%)])</th>
<th>Frequency</th>
<th>Allele1</th>
<th>Frequency (%)</th>
<th>Allele2</th>
<th>Frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>hMSH2</td>
<td>50 (52.1)</td>
<td>41 (42.7)</td>
<td>5 (5.2)</td>
<td>T</td>
<td>73.4</td>
<td>C</td>
<td>26.6</td>
<td></td>
</tr>
<tr>
<td>hMLH1–1151</td>
<td>86 (89.6)</td>
<td>10 (10.4)</td>
<td>0</td>
<td>T</td>
<td>94.8</td>
<td>A</td>
<td>5.2</td>
<td></td>
</tr>
</tbody>
</table>

*For variant.
Discussion

For decades, the prognostic classification has remained unchanged. Disease stages and performance status are the most critical factors to provide a discrimination of prognosis and prediction in NSCLC. However, there are several major limitations to this approach: NSCLC is a heterogeneous disease. Patients have similar clinical and pathological features, but the outcome varies: some are cured, whereas in others, the cancer recurs or aggravates [27]. Furthermore, obtaining of tumor material is not easy in the setting of advanced disease, which is always not resected smoothly and accurately using the small needle biopsy. Therefore, it adds difficulty in the routine clinical setting to make prediction or prognosis using tumor tissue. On the contrary, the evaluation of germline genetic polymorphisms is potentially useful in the clinical setting only with a single blood test.

It is known that platinum-based drugs inhibit tumor growth mainly by the formation of bulky DNA adducts, and the latter are mainly removed by the DNA repair mechanisms, especially by the nucleotide excision repair mechanisms. In fact, our team has already done some work about the association of DNA repair gene polymorphisms and platinum-based chemotherapy [28]. In this study, we assessed the role of two DNA MMR gene polymorphisms, hMSH2 gIVS12-6 and hMLH1-1151, in the response of advanced NSCLC patients treated with platinum-based agents. To elucidate the results more clearly, we separate all patients into two parts according to different stages such as stages III and IV. The main reason for the choice of these two MMR genes was that their crucial and interesting roles in DNA repair, which are necessary and well-founded to be evaluated in NSCLC.

We demonstrated that a T to C transition of the hMSH2 gIVS12-6 gene was statistically significantly associated with response to the platinum-based regimen. The homozygous C/C genotype had much better response than the wild T/T genotype by 3.64 folds. In addition, we also found that there was a trend that in the heterozygous but was not statistically significant ($P > 0.05$).

It was identified that exon 13 of hMSH2 was located in the most conserved region of the gene and encoded part of the DNA-binding domain [29,30]. Although the genetic function of the T to C transition polymorphism at position 6 of the intronic splice acceptor site of exon 13 has not been determined, the variant hMSH2 sequence might weaken the splice site recognition and alter the efficiency of RNA splicing [31–33]. In accordance with above hypothesis, Wang and his colleagues [34] showed a near trend of association with the homozygous C/C variant genotype with the reduced expression of hMSH2 protein in the tumor of NSCLC patients. And many researches had reported that the down-regulation or mutations in hMSH2 were often observed consistently in cisplatin resistance [17,35,36]. In this study, however, the results are opposite to these researches. Although restored DNA repair capacity has beneficial effect on lung cancer survival, impaired DNA repair capacity may favorably affect survival in platinum-based treated NSCLC patients. We think lung cancer patients with low hMSH2 expression may benefit more than those with high hMSH2 expression from adjuvant platinum-based chemotherapy. On the other hand, it is possible that such a finding might be attributed to chance because of the relatively small numbers of subjects in the subgroups. We hope that future larger studies with more patients will be carried out to confirm this finding.

hMLH1, another important MMR gene, was reported to be closely involved in the hereditary non-polyposis colorectal cancer [37,38]. And mutations in gene hMLH1 were also observed consistently in cisplatin resistance. However, in this study, we found no significant association between

<table>
<thead>
<tr>
<th>Genotype</th>
<th>n</th>
<th>Response to chemotherapy</th>
<th>OR (95% CI)</th>
<th>$P$-value</th>
<th>Adjusted OR (95% CI)</th>
<th>Adjusted $P$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>hMSH2 gIVS12-6</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T/T</td>
<td>50</td>
<td>11 (39.3)</td>
<td>39 (57.4)</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>T/C</td>
<td>41</td>
<td>13 (46.4)</td>
<td>28 (41.2)</td>
<td>0.693 (0.348–1.281)</td>
<td>0.2958</td>
<td>0.481 (0.176–1.315)</td>
</tr>
<tr>
<td>C/C</td>
<td>5</td>
<td>4 (14.3)</td>
<td>1 (1.5)</td>
<td>0.275 (0.139–0.544)</td>
<td>0.0166</td>
<td>0.046 (0.004–0.580)</td>
</tr>
<tr>
<td>hMLH1-1151</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T/T</td>
<td>86</td>
<td>23 (82.1)</td>
<td>63 (92.4)</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>T/A</td>
<td>10</td>
<td>5 (17.9)</td>
<td>5 (7.6)</td>
<td>0.534 (0.262–1.010)</td>
<td>0.1497</td>
<td>0.315 (0.066–1.489)</td>
</tr>
<tr>
<td>A/A</td>
<td>0</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

Adjusted OR (95% CI): OR (95% CI) after adjusting for patient gender, age at diagnosis, tumor histology, disease stage, and chemotherapy regimens.

CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease.

Table 4 Genotype and response to chemotherapy among NSCLC patients
the hMLH1-1151 polymorphism and the platinum-based treatment response. It was possible that there were no homozygous genotypes in 96 NSCLC patients and the few numbers of heterozygous genotype: only 10 patients. Intriguingly, it was in agreement with previous studies that there was few mutation of hMLH1 in the tissue of NSCLC [39]. And prospective, large-scale, multicenter studies should be carried out to test this idea.

Traditionally, commonly used genotyping methods including TagMan assay, PCR-RFLP (restriction fragment length polymorphism), and $5'$ nuclease allelic discrimination assay, all of which have limitations in their costly material or lack of powerful high-throughput and could not be used for the identification of all wanted genotyping. To our excitement, the 3D polyacrylamide gel-based DNA microarray method has been demonstrated to have good power in genotyping especially in large-scale samples. There are two main reasons: first, this improved gel-based DNA microarray method could provide a volume, rather than a surface, to enable a larger number of moles of target in the spot and to enhance sensitivity over planar surfaces for microarrays using fluorescence detection polyacrylamide; second, gel improves the local environment of immobilized DNA at the solid-liquid interface to resemble a homogeneous liquid phase reaction rather than a heterogeneous liquid-solid interface reaction [40].

Our analysis included a highly homogeneous cohort of NSCLC patients (only stages III and IV) that might have contributed to highlight the relevance of these variants in the response to platinum. Furthermore, it is more convenient for us to identify different response in different stages. However, the limitations of our study must be acknowledged. First, in this retrospective study, it may be more precise and objective to evaluate the OS and progression-free survival (PFS) as prognostic factors. Because the patients for this study were recruited between March 2006 and September 2007, it would be better that the analysis about OS and PFS is taken at least 5 years later. On the other hand, considering difficulty in clinical practice, we chose chemotherapy response as end point of prediction, which was also critical to illuminate the mechanism by which DNA repair affect the outcome. Ideally, prospective validation studies should be carried out to measure such parameters as predictive and prognostic factors, which will be our expected outcome of next research. Second, although this study comprised 165 candidates, only 96 patients were compatible with this study, and it may because of the relatively short-time for sample collection and the limitation to be generalized in NSCLC. Platinum-based chemotherapy as a combination received by 96 patients, there is a question whether these chemotherapeutics would interact with each other. It is noteworthy that the MMR proteins demonstrate greater preference for cisplatin adducts than for adducts induced by distinct platinum analogs that may contribute to different results. If the same chemotherapeutic regimens had been used in the treatment, the predictive role of SNP might would been generalized more credibly.

In summary, to the best of our knowledge, the present study is the first to report the association of the homozygous hMSH2 C/C genotype and better response to platinum-based chemotherapy in NSCLC. Furthermore, the polymorphic status of hMSH2 C/C might be a predictive factor in treatment response of advanced NSCLC patients. Also, we first by using the 3D DNA microarray method, an efficient, rapid, and simple test, documented that the hMSH2 genetic polymorphisms are associated with response to chemotherapy with single blood. More well-designed, larger, and prospective studies will be necessary to further help define their role and value in the conventional treatment setting for patients with NSCLC.

Funding

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References

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