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Pharmacogenomics: A reality or still a promise?

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Summary

Although notable progress has been made in the treatment of non-small-cell lung cancer (NSCLC) in recent years, this disease is still associated with a poor prognosis for most patients. Modern techniques have facilitated the identification of specific genetic factors that may play a role in disease progression and patient response to therapy, prompting research efforts to identify the clinical predictors of outcome for NSCLC. Recent evidence suggests that the application of a pharmacogenomic approach has the potential to greatly improve survival in certain subpopulations of patients with NSCLC, which could profoundly influence the decision-making process used in evolving treatment strategies for this malignancy.

Keywords

Chromosome 11p15.5; *ERCC1*; gemcitabine; immunohistochemistry; NSCLC; pharmacogenomics; *RRM1*

Genomic abnormalities in lung cancer

The genome of cancer cells, as identified by modern, sophisticated techniques that can pinpoint chromosome breaks and rearrangements, is extremely complex. The predominant type of genome instability in cancer is structural aberration of chromosomes, such as deletions, translocations, and insertions, which may arise due to impaired repair of DNA double-strand breaks [1,2] [Rouet 1994, Liang 1998].

Loss-of-heterozygosity (LOH) analysis is the most frequently used technique to assess genomic aberrations [3] [Bepler 2002]. The identification of allele loss with this technique has led to the discovery of numerous genes with key functions in tumour development and progression [4] [Pitterle 1998].

Molecular genetic studies have detected many chromosomal regions with frequent LOH in lung cancer, including areas on chromosomes 3, 5, 8, 9, 11 and 17 [4–8] [Bepler 1994, Whang-Peng 1982, Takahashi 1989, Naylor 1987, Pitterle 1998]. The identification of frequent allele loss on chromosome 11p15.5 in NSCLC prompted investigations to identify and characterise tumour-suppressor genes with potential involvement in the development and progression of this disease [5] [Bepler 1994]. LOH in this region has since been linked to patient outcome in NSCLC, and is highly predictive of poor survival [3] [Bepler 2002].

RRM1, a gene in the 11p LOH region

Following the identification of its potential role in NSCLC, the centromeric part of the 11p15.5 chromosome segment, known as *LOH11A*, was mapped and sequenced [9–10] [Bepler 1999,

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Zhao 2001], and positional cloning studies identified the putative tumour suppressor gene, *RRM1*, within this region [11] [Pitterle 1999].

Early genetic complementation studies with chromosome 11 strongly suggested that a gene, or genes, in the *LOH11A* region inhibited tumourigenicity in nude mice and growth in liquid culture [12] [O'Briant]. Subsequently, it was demonstrated that the *RRM1* gene suppresses invasion, migration and *in vivo* metastasis formation through up-regulation of the *PTEN* tumour suppressor gene when overexpressed in human and mouse lung cancer cell lines [13] [Gautam 2003]. In a recent transgenic mouse study, mice continuously overexpressing *RRM1* were found to be less susceptible to carcinogen-induced lung cancer formation and displayed improved survival compared with control mice [14]. [Gautam A, Bepler G 2006] Splenocyte assays revealed that transgenic *RRM1* overexpressing mice had a higher capacity to repair DNA damage, which could explain the observed reduction in susceptibility to lung tumour induction.

These *in vitro* and *in vivo* observations suggest that overexpression of *RRM1* results in a more 'benign' phenotype and could, therefore, be a significant predictor of survival in NSCLC. This hypothesis was investigated through the study of retrospective and prospective datasets of patients with resectable NSCLC [15] [Bepler 2004]. This analysis concluded that *RRM1* is a biologically and clinically important determinant of malignant behaviour in NSCLC and represents a strong predictor of outcome in patients with resectable disease. It was also suggested that future randomised trials of NSCLC should stratify patients based on *RRM1* expression since tumours with high levels of expression have an intrinsically less malignant phenotype.

RRM1 is the molecular target of gemcitabine

The inherent or induced resistance of tumours to cytotoxic agents represents a major clinical problem. Several recent publications have highlighted a possible link between *RRM1* expression and increased resistance to the antimetabolite gemcitabine in NSCLC [16–19] [Bergman 2002, Davidson 2004, Bergman 2005, Bepler 2006 Clin Oncol 2006.

Ribonucleotide reductase is the rate-limiting enzyme in DNA synthesis, and it is the only known enzyme that converts ribonucleotides to deoxyribonucleotides, which are required for DNA synthesis and repair. The ribonucleotide reductase holoenzyme consists of two dimerised subunits (*RRM1* and *RRM2*), the pairing of which is essential for deoxynucleotide synthesis. Although the physical relationship between gemcitabine and mammalian ribonucleotide reductase has not been well characterised, data support the hypothesis that the *RRM1* subunit is the most likely intracellular target for gemcitabine diphosphate [17,20] [Fan 1997, Davidson 2004]

Davidson et al. identified increased expression of *RRM1* as the major determinant of gemcitabine resistance [17] [Davidson 2004] In 2005, Bergman et al. developed the first *in vivo* model of resistance to gemcitabine as a result of repetitive treatment using a clinically relevant schedule. In line with previous *in vitro* studies, microarray profiling revealed a marked increase in *RMM1* expression, and, therefore, identified this gene as a key target for acquired *in vivo* gemcitabine resistance [18] [Bergman 2005]. These observations clearly indicate that R*MM1* could play a role in the prediction of patient outcome, and draw attention to the fact that response to gemcitabine represents an area of research where the application of pharmacogenomics could be of vital importance. The challenges faced by this emerging model include determination of whether its application improves treatment response and survival, while reducing the toxicity experienced by patients.

Current approaches to lung cancer therapy

Platinum-based combination therapy is the established standard of care for the first-line treatment of advanced NSCLC. Although the current practice for treating patients with metastatic disease includes the addition of newer generation agents such as vinorelbine, gemcitabine, paclitaxel or docetaxel to a platinum agent, no combination has emerged as a gold standard [21 [Fossella 2003]. Recent, large Phase III trials comparing modern platinum-based regimens in the first-line treatment of advanced NSCLC found no clear advantage for any regimen [22–25] [Schiller 2002, Kelly 2001, Belani 2005, Rosell 2002]. Similarly, studies investigating non-platinum doublets versus platinum doublets were unable to demonstrate significant differences in outcome [26–29] [Georgoulias 2001, Kosmidis 2002, Gridelli 2003, Smit 2003].

Most recently, trials have investigated the addition of molecularly targeted agents such as gefitinib (INTACT-1 and -2 trials) [30–31] [Giaccone 2004, Herbst 2004] and erlotinib (TALENT and TRIBUTE trials) [32–33] [Gatzemeier 2005, Herbst 2005] to cytotoxic chemotherapy regimens in untreated patients with advanced NSCLC, but no benefit in terms of increased response rate, time to progression or overall survival has been demonstrated. The one exception is bevacizumab, which recently became the first targeted therapy to demonstrate superior efficacy combined with standard doublet chemotherapy over chemotherapy alone in the treatment of NSCLC, although this is based on preliminary data [34] [Sandler 2005]

Therefore, although it remains the key treatment modality, the one size fits all approach to first-line chemotherapy of NSCLC appears to have reached a therapeutic plateau. Currently, subgroups of NSCLC patients that might have different responses to treatment are primarily defined on the basis of clinical parameters such as performance status, personal preference, convenience, central nervous system metastases, histology, bleeding disorders, gender and smoking status. However, pharmacogenomics has the potential to allow the selection of specific patients on a genetic basis. It is hypothesised that this specific tailoring of therapy, guided by individual patient genetics, could lead to unequivocally superior responses following chemotherapy treatment.

RRM1- and *ERCC1*-based chemotherapy selection

As outlined earlier in this article, the available evidence indicates that if *RRM1* is highly expressed (within physiological range) in genetically modified cell lines, resistance to gemcitabine increases, and, if *RRM1* is not highly expressed, cell lines become sensitive to gemcitabine (Figure 1). [19] [Bepler 2006]

Since it has been demonstrated that *RRM1* has an impact on DNA damage and repair, it would be expected to have an influence on the activity of other drugs, particularly the platinum agents. *In vitro* studies have identified a minor but consistent impact of *RRM1* on platinum chemosensitivity, with increased *RRM1* levels making cells slightly more resistant to carboplatin (Figure 2) [19] [Bepler 2006]. Evidently, this could have significant implications for platinum combination chemotherapy.

Two exploratory retrospective datasets investigating this hypothesis in patients with stage IV NSCLC have provided evidence that *RRM1* mRNA expression is a crucial predictive marker of survival in patients treated with gemcitabine plus cisplatin [35–36] [Rosell 2003, Rosell 2004]. Although these studies have certain limitations due to their retrospective nature and size, and the fact that no assessable impact on disease response was documented, the observed effects on survival suggest that genetic testing of *RRM1* mRNA expression levels can and should be used to personalise platinum-based chemotherapy [36] [Rosell 2004]

The second of these studies also showed that the excision-repair cross-complementing group 1 (*ERCC1*) gene is related to cisplatin activity, [Rosell 2004] and other studies have confirmed that lung cancer is a malignancy in which the expression of this excision nuclease is directly related to the outcome of DNA-damaging therapy [37–38] [Reed 2005, Lord 2002]

Based on the evidence that *RRM1* and *ERCC1* may result in chemoresistance, two prospective Phase II trials were initiated, the results of which will be published in the near future. The goal of the first study (MCC-13240) was to obtain tumour biopsies under optimal conditions and measure *RRM1* and *ERCC1* expression to determine whether there is a direct correlation with response to gemcitabine plus carboplatin in patients with locally advanced stage IIIa and IIIb NSCLC [39]. The aim of the second trial (MCC-13208), referred to as the Molecular Analysis-Directed Individualized Treatment for Advanced NSCLC (MADeIT) trial, was to tailor chemotherapy based on the expression of these genes.

Following two cycles of chemotherapy with gemcitabine plus carboplatin, data from 35 patients in the MCC-13240 trial revealed a highly significant correlation between high levels of *RRM1* expression and poor treatment response. Similarly, low levels of *RRM1* expression were associated with an increased likelihood of patient response. The same trend was observed for *ERCC1*expression, although statistical significance was not reached.

In the MADeIT study, chemotherapy was administered based on the level of expression of *RRM1* and *ERCC1*. Patients with stage III/IV disease had dedicated tumour biopsies, and, if high levels of *RRM1* expression were identified, the patients received a chemotherapy doublet not containing gemcitabine, while those with low levels of *RRM1* expression were given a doublet that included gemcitabine (see Figure 3).

The goal of this study was not to compare different treatments, but to demonstrate that upfront patient selection can lead to the administration of the most suitable treatment, which should, theoretically, result in the best possible outcome. This was found to be the case, with data indicating an unprecedented 12-month survival rate of 62%. Comparison with another study (MCC-12621) conducted at the same institution by the same physicians and with matching referral patterns, staging and enrolment criteria revealed that results obtained in the MADeIT study were close to 50% better (Table 1) [40]. Similarly, results from another study (E1594) revealed that the tailored treatment used in the MADeIT trial produced 12-month survival values that were almost double those previously observed [22].

Development of immunohistochemistry for determination of *RRM1* and *ERCC1* expression

Clearly, the method of treatment selection used in the above-mentioned studies holds tremendous promise. However, this approach currently represents a boutique therapy since the expression analysis techniques used require a substantial infrastructure and, therefore, may not be readily accessible to the vast majority of patients.

However, recent evidence suggests that *ERCC1* and *RRM1* expression can be determined using immunohistochemistry, and preliminary results indicate that data obtained with this technology are consistent with values produced by real-time quantitative polymerase chain reaction. Soria et al. recently used a standard protocol of immunohistochemistry to confirm that patients with completely resected NSCLC and *ERCC1*-negative tumours derive a substantial benefit from adjuvant cisplatin-based chemotherapy. [Soria 2006] [41] Since this powerful antibody staining technique is simple to carry out and results can be easily interpreted, it could be widely used in the clinic. In addition, triple-staining automated systems, which eliminate potential

errors due to subjectivity, have recently been developed to analyse *RRM1*, highlighting that immunohistochemistry has a vital role to play in the prediction of pharmacogenomic responses.

Conclusion

Due to the extremely complex nature of the genome of cancer cells, new discoveries are continually being made in this exciting field of research. Pharmacogenomics centres on the principle that these molecular genetic findings have the potential to ultimately affect therapeutic decisions in the clinic and greatly improve the treatment benefits experienced by patients. The available evidence clearly indicates that the identification and exploitation of genetic markers, predictive of response to specific cytotoxic drugs, is an achievable goal, and should, therefore, become a priority of current cancer research and future trials. Early results indicate that the application of pharmacogenomics in the field of NSCLC has the potential to profoundly influence outcomes and greatly improve survival in this fatal malignancy.

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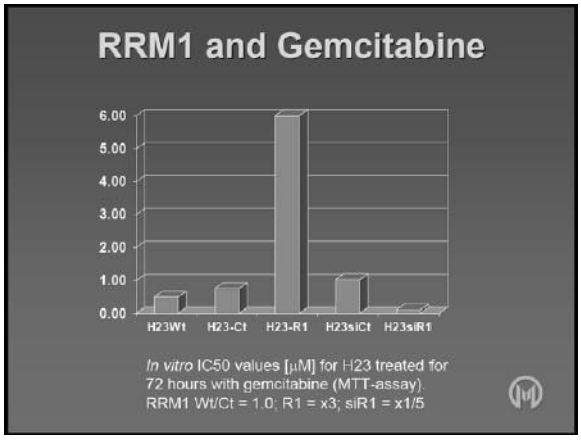

Figure 1.
Effect of *RRM1* levels on gemcitabine *in vitro*.

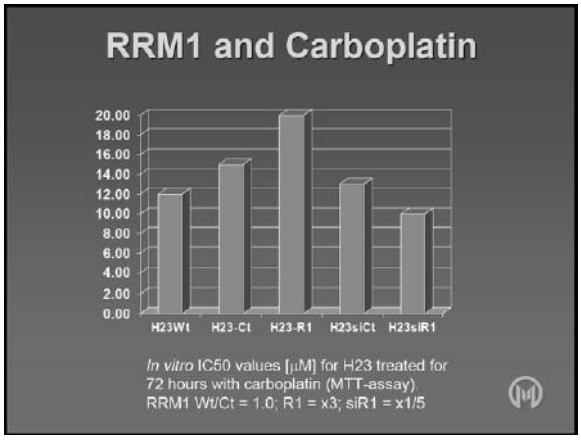

Figure 2.
Effect of *RRM1* levels on carboplatin *in vitro*.

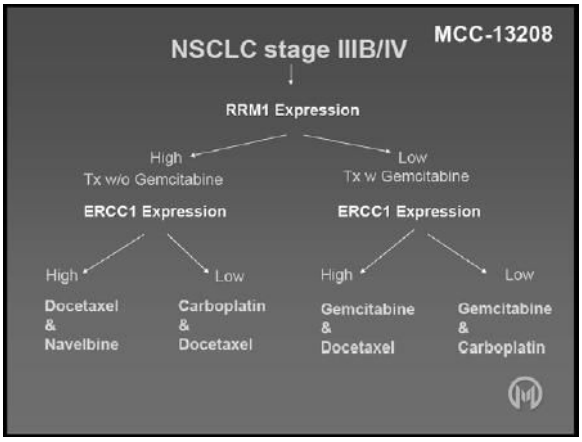

Figure 3.
Study design for the MCC-13208 (MADeIT) trial.

Table 1

Comparison of results from the MCC-13208 (MADeIT), 12621 and E1594 trials.