ERCC1 Codon 118 Polymorphism Is a Predictive Factor for the Tumor Response to Oxaliplatin/5-Fluorouracil Combination Chemotherapy in Patients with Advanced Colorectal Cancer

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Abstract

Purpose: The aim of our study was to assess whether the polymorphism of the nucleotide excision repair enzyme, excision repair cross-complementing rodent repair deficiency, complementation group 1 (ERCC1), had an effect on the tumor response in patients treated with standard chemotherapy regimens for a metastatic colorectal cancer. We have studied the synonymous polymorphism that causes a single nucleotide change C to T at codon 118 converting a codon of common usage (AAC) to a less used codon (AAT), both coding asparagine. This change results in a decreased *ERCC1* gene expression, which impairs repair activity.

Experimental Design: Ninety-one patients with a median age of 55.1 years treated for a metastatic colorectal cancer were included in our retrospective study. The *ERCC1* polymorphism was analyzed in the normal tissue of all patients.

Results: Twenty (22%) were homozygous for AAC codon (*C*/*C* genotype), 30 were (33%) homozygous for AAT codon (*T*/*T* genotype), and 41 (45%) were heterozygous (*C*/*T* genotype). The objective response rate to oxaliplatin in combination with 5-fluorouracil (5-FU) was significantly higher in the *T*/*T* genotype group compared with the *C*/*T* and the *C*/*C* genotype groups (61.9%, 42.3%, and 21.4%, respectively; $P = 0.018$). By contrast, no significant difference was observed when patients were treated with either 5-FU alone (45%, 29.2%, and 33.3%, respectively; $P = 0.407$) or in combination with irinotecan (46.1%, 25.0%, and 27.3%, respectively; $P = 0.305$).

Conclusions: Our observations allowed us to define the first useful predictive criterion for oxaliplatin/5-FU response in patients with metastatic colorectal cancer.

Colorectal cancer is one of the most common adult malignant tumors. In Northern-America and Western Europe, the standardized incidence is 24.6 and 39.1 cases/100,000/y for women and men, respectively. About half of the patients develop metastasis or recurrent disease (1). Some patients may be cured with surgery, but most of them need a chemotherapeutic treatment. The different regimens used consist in 5-fluorouracil (5-FU) modulated with folinic acid, alone or in combination with oxaliplatin, a diaminocyclohexane platinum, or irinotecan, a topoisomerase I inhibitor. The antitumor activity of these combinations as first- or second-line treatment for advanced metastatic colorectal cancers has been investigated in large phase II and III trials (2–5). These combinations are more effective, with an objective response rate close to 55% in metastatic colorectal cancer first-line treatment compared with the 20% to 30% objective response rate of 5-FU common regimens (6). Unfortunately, no predictive factor of response to these treatments is yet available in clinical practice.

The nucleotide excision repair system plays a major role in repairing a variety of distorting lesions, notably platinum-induced DNA adducts (7). Oxaliplatin is a platinum-based therapeutic agent that has shown *in vitro* and *in vivo* antitumor activities in colorectal cancer, where other platinum compounds, cisplatin and carboplatin, have failed to show any activity (8). Oxaliplatin carries a 1,2-diamino-cyclohexane ring leading to DNA damage by forming DNA-platinum monoadducts with guanines that are converted in diadducts overtime. In contrast to cisplatin, oxaliplatin-induced adducts are apparently not recognized or processed by mismatch repair, being predominantly repaired by the nucleotide excision repair pathway (9, 10).

During nucleotide excision repair, the damaged DNA is recognized by xeroderma pigmentosum group C complementing protein (XPC)-hHR23B heterodimer, which recruits transcription factor IIH, XPA, and replication protein A. Then, the helicases XPB and XPD, components of the transcription factor

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IIH complex, separate the damaged strand from the undamaged, and the nucleases XPG and XPF-excision repair cross-complementing rodent repair deficiency, complementation group 1 (ERCC1) cleave at 3′ and 5′ to the damage, respectively, removing a 27- to 30-mer oligonucleotide containing the modified nucleotides. The release of the damaged oligonucleotide allows a new strand of DNA to be synthesized by the replication polymerases Pol δ and Pol ε, recovering an intact strand followed by ligation (7). Among the ~30 identified polypeptides that participate in the nucleotide excision repair process, the ERCC1 protein has a crucial role in the incision process by stabilizing the XPF endonuclease.

As expected, ERCC1 has been reported to play a major role in the response to platinum-based therapies. The mRNA level of *ERCC1* has been shown to correlate with nucleotide excision repair capacity in human lymphocytes, bone marrow, and brain tissue (11–14). Chinese hamster ovary cells, which do not express a functional ERCC1 protein, are more susceptible to these drugs than the parental cell line with normal ERCC1 (15, 16). Therefore, one could expect that the higher the levels of expression of ERCC1, the less susceptible the tumors to platinum therapies. The possibility that a defect in nucleotide excision repair results in hypersensitivity to oxaliplatin may be particularly relevant to the treatment of colorectal cancer, especially because specific predictive criteria for oxaliplatin activity are still lacking. Interestingly, a synonymous polymorphism at codon 118 converting a common codon usage (AAC) to an infrequent one (AAT), both coding for asparagine, has recently been proposed to impair *ERCC1* translation and to affect the response to cisplatin chemotherapy (17, 18).

Besides its predominant role in nucleotide excision repair, ERCC1 is involved in other cellular processes. *ERCC1* knockout mice are runted at birth and die before weaning due to liver failure, an unusual phenotype that is shared with *XPF* knockout mice, but not with any of the other nucleotide excision repair–deficient mice (19–21). In mammals, the ERCC1 protein also acts in a complex with XPF to remove nonhomologous 3′ ends in the single-stranded annealing pathway of homologous recombination (22). ERCC1 acts in homologous recombination not only in the removal of nonhomologous tails but also in homology-dependent gene targeting events (23, 24). *ERCC1*-null mouse embryonic fibroblasts are extremely sensitive to interstrand cross-linking induced by agents such as mitomycin C, a DNA damage thought to be repaired by a mechanism involving homologous recombination (25). Interestingly, in yeast, the covalent complex formed between DNA, topoisomerase I, and camptothecin can be removed by Rad1/Rad10, the human orthologue of which is the XPF/ERCC1 complex (26).

The aim of our study was to investigate whether the *ERCC1* codon 118 polymorphism influenced the response to treatment with oxaliplatin or irinotecan in patients with metastatic colorectal cancer. Yet, the possibility of individualizing DNA repair profiles is becoming a central issue to improve chemotherapy strategies (27, 28).

Patients and Methods

Demographics of patients and tumor sample selection. This study was carried out with the Institutional Ethics Committees approval and following the French Medical Research Council guidelines. Ninety-one patients treated for metastatic colorectal cancer at the Gustave Roussy Institute in Villejuif, France, from June 1995 to June 2002, were included in this retrospective study (Table 1). They consisted of 34 women (37.4%) and 57 men (62.6%), with a median age of 55.1 years (interquartile range, 48.3-62.3). The other patient clinical characteristics are reported in Table 1. Tumor samples were taken from the primary colonic or rectal tumor or from liver metastasis. Normal samples were taken from adjacent normal colon, rectum, or liver normal tissue.

Chemotherapy treatments. A total of 154 treatments were analyzed. These treatments consisted of oxaliplatin (Eloxatine, Sanofi-Synthelabo, Gentilly, France), 85 to 100 mg/m^2 in combination with 5-FU once every 2 weeks, and irinotecan (Campto, Aventis, Antony, France) alone (300-350 mg/m^2) every 3 weeks or in combination (180 mg/m^2) with 5-FU once every 2 weeks. 5-FU was used in a regimen with 200 mg/m^2 bolus, then 400 mg/m^2 continuous infusion, day 1 and day 2, every 2 weeks, modulated by folinic acid. The treatment was given until disease progression, unacceptable toxicity, or patient's refusal to continue treatment.

Chemotherapy response criteria. All patients had a bidimensionally measurable CT scan lesion at the time of the treatment initiation. The end point was the tumor response to chemotherapy evaluated according to the WHO criteria (29). An objective response to the treatment corresponded to a complete (disappearance of the disease) or partial (at least 50% reduction in tumor load of the lesions) response. Patients with stable disease (≤25% progression, <50% shrinkage) or cancer progression (size enlargement >25% or appearance of new lesions) were classified as nonresponders. The clinicopathologic characteristics of the patients included in our study are shown in Table 1.

DNA extraction. Both normal and tumor tissues were studied. Genomic DNA was extracted from 20-μm-thick tissue sections from normal tissue primary tumors or metastatic lesions stored in liquid nitrogen. Seven frozen samples were lacking and required the use of 7 μm paraffin-embedded tissue sections. Areas of normal and tumor tissue were previously delineated for each sample by microscopic examination of a reference slide stained with H&E. Extraction was done using the DNeasy Tissue Kit (QIAGEN, Hilden, Germany). About 1 cm^2 tissue was scraped and transferred into a 1.5 mL tube. The tissues were

Table 1. Demographics of the 91 patients

Variables	*n* (%)
Sex (female/male)	34/57 (37.4/62.6)
Median age [interquartile range]	55.1 [48.3-62.3]
Primary tumor site	
Proximal colon	22 (24.2)
Distal colon	49 (53.9)
Rectum	20 (22.0)
Metastases	
Synchronous	58 (63.7)
Metachronous	33 (36.3)
Number of organs involved	
1	69 (75.8)
2	17 (18.7)
3	5 (5.5)
Main organs involved	
Liver	75 (82.4)
Peritoneum	20 (22.0)
Lung	12 (13.2)
Lymph node	8 (8.8)
Ovary	3 (3.3)

Table 2. Chemotherapy regimen according to the line of treatment

	Number of treatments for each chemotherapy regimen			Total
	5-FU	Oxaliplatin + 5-FU	Irinotecan + 5-FU	
	n (%)	*n* (%)	*n* (%)	*N*
First line	50 (54.9)	29 (31.9)	12 (13.2)	91
Second line	3 (5.9)	29 (56.9)	19 (37.2)	51
Third line	0 (0.0)	3 (25.0)	9 (75.0)	12
All lines	53 (34.4)	61 (39.6)	40 (26.0)	154

incubated for 3 hours at 55°C in a buffer containing 200 μg/mL proteinase K, which was subsequently inactivated by a 10-minute incubation at 70°C. About 4 to 6 μg of genomic DNA were finally extracted for each of normal and tumor samples, with a DNA final concentration evaluated at 25 ng/μL, and stored at 4°C until use.

ERCC1 codon 118 polymorphism genotyping. This analysis was done using DNA amplification followed by digestion with the restriction enzyme *Bsr*DI that specifically cuts the codon 118 *T* allele. The first step consisted of the amplification of the DNA region encompassing codon 118 (exon 4) in a PCR using two sets of primers. A 1,445 bp region was amplified using 5′-GTAGCTCTGTTTCCT-CACCCCAGG-3′ and 5′-AGCAGGGCCCACTGCCAAACCATC-3′ as primers. In case of amplification failure with these primers, a 413 bp fragment was amplified using 5′-GTGCGAGGAGGCAG-GAGGTGTGGG-3′ and 5′-TGTTGCACTGGGCACCTCCAGGCC-3′ as primers, surrounding more proximately the *ERCC1* codon 118. A first round of PCR was done on 25 ng genomic DNA in a total volume of 20 μL using 200 μmol/L deoxynucleotide triphosphate (Amersham Biosciences AB, Uppsala, Sweden) and 0.5 unit of HotStar Taq DNA polymerase (Qiagen), using each primer at 400 nmol/L final concentration. After an initial 15-minute denaturation step at 95°C, amplification was achieved by 50 cycles consisting of 1-minute denaturation at 94°C, 1-minute annealing at 64°C, and 2-minute elongation at 72°C, followed by a final 10-minute elongation step at 72°C. PCRs were repeated twice to confirm the results. Ten microliters of the PCR products were digested with *Bsr*DI for 4 hours at 65°C in a final volume of 20 μL with 2 units of *Bsr*DI in a 10 mmol/L Tris-HCl buffer at pH 7.9, containing 50 mmol/L NaCl, 1 mmol/L DTT, and 20 μg bovine serum albumin. The 1,445 and 413 bp fragments were cleaved by *Bsr*DI in two fragments of 858 and 587 bp and 253 and 160 bp, respectively. Digestion products were then migrated in a 1% agarose gel in the presence of ethidium bromide.

Statistical analyses. The associations between the tumor responses and the polymorphism status were assessed considering chemotherapy regimens independently and jointly. When chemotherapy regimens were studied independently, a Cochran-Armitage χ^2 test for trend was used to assess whether there is a significant association between the number of *ERCC1* codon 118 *T* allele copy and the response rate. When the three chemotherapies were analyzed jointly, a marginal model using the binomial distribution and the logit as the link function was used to take into account correlation in data.

Results

Patients analyses. All 91 patients selected were eligible for the data analyses and consecutively included in this study. They all received a 5-FU–based chemotherapy in first-line treatment, alone (54.9%) or in combination with oxaliplatin (31.9%) or irinotecan (13.2%). About 54% of the patients had a second-line treatment and 13% a third one. A combination of drugs was used in most cases (93.9%) in second-line treatment, and in all cases in the third line (Table 2). All patients were assessable to test the possible association between the *ERCC1* codon 118 polymorphism and the response to chemotherapy using the above-cited criteria.

Polymorphism of ERCC1 codon 118. Amplification of the 1,445 bp fragment was successful for all DNA prepared from nitrogen-preserved samples. It failed for three samples extracted from paraffin-embedded tissues, which were successfully amplified with the second couple of primers giving a 413 bp fragment.

The analysis of the polymorphism located at *ERCC1* codon 118 in the normal tissue showed that 20 (22%) were homozygous for the AAC codon (*C/C* genotype), 30 (33%) were homozygous for the AAT codon (*T/T* genotype), and 41 (45%) were heterozygous (*C/T* genotype). The prevalence of the *T* and *C* alleles at codon 118 were 55.5% and 44.5%, respectively.

Although the 19q13 chromosomal region that harbors the *ERCC1* gene is not frequently rearranged in metastatic colorectal cancer, we were interested in defining whether loss of *ERCC1* heterozygosity occurred in tumors. To detect a possible loss of one allele in the tumor, the same analysis was done in the tumor tissue from the 41 patients with the *C/T ERCC1* codon 118 genotype and was compared with the corresponding normal tissue genotype. Loss of one allele was observed in the tumor tissue of one patient (2.4%), in which only the *C* allele remained detectable.

Response to chemotherapy in relation to the ERCC1 codon 118 polymorphism. Based on the reports showing that protein expression of the *ERCC1 T* allele is lower than that of the *C* allele, patients were segregated into three groups (30). The "low *ERCC1* expressing" group consists of the 30 *T/T* homozygous patients; the "intermediate *ERCC1* expressing" group includes the 41 *C/T* heterozygous patients; and the "high *ERCC1* expressing" group consists of the remaining 20 *C/C* homozygous patients. Chemotherapy responses were analyzed according to these three groups (Table 3).

A total of 154 first-, second-, or third-line treatments could be analyzed in our series of 91 patients. In the *T/T* genotype group, 54 treatments were evaluated, consisting of an objective response (complete or partial) in 28 (51.8%) cases and a stable or a progressive disease in the remaining 26 (48.2%) cases. Sixty-six treatments were analyzed in the *C/T* genotype group, consisting of 22 (33.3%) objective responses and 44 (66.6%) cases for whom treatment was inefficient. The same analysis done for the 34 treatments evaluated in the *C/C* genotype group showed 9 (26.5%) objective responses and 25

(73.5%) stable or progressive diseases. Thus, our results show that the response to chemotherapy was significantly better in the *T/T* genotype group ($P = 0.033$) when all regimens are analyzed jointly in the framework of a marginal model using the binomial distribution and the logit as the link function. Expressed as odds ratio of objective response, and with an odds ratio of 1 for the *C/C* genotype group, the result for the *C/T* genotype group was an odds ratio of 1.42 (95% confidence interval, 0.52-3.86; $P = 0.49$) and for the *T/T* genotype group an odds ratio of 3.03 (95% confidence interval, 1.09-8.40; $P = 0.033$).

The overall objective response rate to 5-FU alone was 35.8%, and reached 44.3% in combination with oxaliplatin and 32.5% in combination with irinotecan. The response rate with oxaliplatin/5-FU was 61.9% in the *T/T* genotype group versus 42.3% in the *C/T* group and 21.4% in the *C/C* group. The relationship between the *ERCC1* phenotype and the response to oxaliplatin/5-FU combination chemotherapy was statistically significant ($P = 0.018$). The response rate for 5-FU regimen was 45% in the *T/T* genotype group, versus 29.2% and 33.3% for the *C/T* and the *C/C* genotype groups, respectively ($P = 0.407$). The response rates for the irinotecan/5-FU combination were 46.1% versus 25.0% and 27.3% for the *T/T* versus *C/T* and *C/C* groups, respectively ($P = 0.305$). The difference between the three groups failed to reach significance with 5-FU alone or in combination with irinotecan.

Discussion

The aim of our study was to determine whether *ERCC1* polymorphism at codon 118 predicts the clinical outcome of patients with advanced colorectal cancers treated with various chemotherapies. The identification of molecular variables that predict either resistance or sensitivity to chemotherapy is of major interest in selecting the most likely effective first-line treatment, avoiding adverse side effects of a toxic but inactive therapy. Interindividual variations in DNA repair ability have been recognized to modulate tumor responses to DNA damage-inducing drugs; notably, nucleotide excision repair activity has been shown to influence platinum-based chemotherapy (31). There is increasing evidence of a relationship between the level of ERCC1 and the response to chemotherapy. Higher mRNA levels of *ERCC1* are associated with resistance of ovarian (32), gastric (33), and colon (34) cancers to chemotherapy with platinum drugs. Clinically, lower mRNA *ERCC1* levels are associated with improved tumor response (32–34).

In this study, we have focused on the synonymous *ERCC1* C→T polymorphism at codon 118 because it has been reported to affect the level of *ERCC1* expression (30). One possible explanation comes from the fact that although both the AAC and AAT codons encode asparagine, the AAT codon usage is significantly reduced, thereby decreasing *ERCC1* translation efficiency and protein level. Because many of the environmental carcinogens cause both monoadducts and intra- or inter-crosslinks in DNA that may be repaired by nucleotide excision repair, single nucleotide polymorphisms in human DNA repair genes may modulate repair activity and be relevant to cancer risk. In our series of patients, the *C* and *T* allele frequencies obtained by genotyping normal DNA are in close agreement with those recently reported in healthy donors and patients with advanced colorectal cancer (35, 36). Some *XPD* gene polymorphisms have actually been shown to increase cancer risk, illustrating the effect of small variations in DNA repair efficacy (37). Furthermore, the *C* and *T* alleles are in Hardy-Weinberg equilibrium, further confirming that variation in *ERCC1* coding sequence is unlikely to significantly predispose to colorectal cancer, as recently reported for a number of nucleotide excision repair genes (38). Another *ERCC1* polymorphism located in the 3′ untranslated region of the gene, which affects mRNA stability, has been associated with gliomas and squamous cell carcinoma of the head and neck (39, 40). It is of note that this *ERCC1* polymorphism also results in an amino acid substitution in *ASE-1* (antisense-*ERCC1*), a gene with no known biological function identified thus far that partially overlaps with *ERCC1*. Thus, whether this *ERCC1* polymorphism itself may be involved in cancer predisposition remains to be established.

Owing to its possible effect on gene expression, it is reasonable to anticipate that *ERCC1* codon 118 polymorphism may influence tumor response to platinum-based chemotherapy. Although *in vitro* studies using various human ovarian carcinoma cell lines confirmed that the *C/C ERCC1* genotype is more effective in repairing platinum-DNA lesions, clinical studies on this issue are still awaiting (30). These observations prompted us to evaluate the effect of the *ERCC1* codon 118 polymorphism on the response of metastatic colorectal cancer to the treatments usually used. In our series, the response rates for the different chemotherapeutic regimens in metastatic colorectal cancer were within the usual range, except for

Table 3. Association between the *ERCC1* codon 118 polymorphism and the response to chemotherapy

Chemotherapy regimens	Global		*T/T* group		*C/T* group		*C/C* group		*P*
	Number of treatments	Objective responses	Number of treatments	Objective responses	Number of treatments	Objective responses	Number of treatments	Objective responses	
	n	n (%)	*n*	n (%)	*n*	n (%)	*n*	n (%)	
5-FU	53	19 (35.8)	20	9 (45.0)	24	7 (29.2)	9	3 (33.3)	0.407
Oxaliplatin + 5-FU	61	27 (44.3)	21	13 (61.9)	26	11 (42.3)	14	3 (21.4)	0.018
Irinotecan + 5-FU	40	13 (32.5)	13	6 (46.1)	16	4 (25.0)	11	3 (27.3)	0.305
All regimens	154	59 (38.3)	54	28 (51.8)	66	22 (33.3)	34	9 (26.5)	

NOTE: The objective response corresponded to a complete (disappearance of the disease) or a partial (>50% reduction in tumor load of the lesions) response to the various treatments.

irinotecan of which global response rate was lower than that obtained with 5-FU, possibly because irinotecan was more often used in third-line treatment. The objective response rates to the treatment with 5-FU alone did not differ according to the *ERCC1* polymorphism status of the patients. The absence of a relationship between *ERCC1* polymorphism and 5-FU resistance is not surprising because ERCC1 is unlikely to play a role in the repair of 5-FU–induced lesions. Indeed, the mechanisms of action of 5-FU involve a competitive inhibition of thymidylate synthase by 5-fluoro-dUMP, the incorporation of 5-fluoro-UTP in RNA affecting their maturation, and the incorporation of 5-fluoro-dUTP in DNA inducing its fragmentation (41). The rate of objective response to irinotecan is higher in patients with homozygous *ERCC1* codon 118 *T/T* genotype, but this difference did not reach significance, possibly because the number of treatments evaluated is too small. The molecular mechanisms that could underlie this difference are not yet clear. The cytotoxicity of irinotecan implies the generation of DNA double-strand breaks (42). Owing to the role of ERCC1 in processing recombination intermediates generated during DNA double-strand break repair, a decrease in *ERCC1* expression may affect recombination repair efficiency, accounting for the higher tumor sensitivity observed in patients with the *T/T* genotype (24). Another hypothesis comes from the observation of a positive correlation between the *ERCC1* mRNA level and the expression of DNA topoisomerase I in ovarian cancer, suggesting a common mechanism of regulation of the expression of these genes (43). Because higher levels of topoisomerase I have been proposed to result in increased cytotoxicity of irinotecan, the possible effect of *ERCC1* polymorphism on topoisomerase I expression deserves further investigation in colorectal cancer. Additional studies are needed to definitely assess the predictive value of the *ERCC1* codon 118 polymorphism for the irinotecan response of metastatic colorectal cancer.

To our knowledge, this is the first study demonstrating that the *ERCC1* polymorphism at codon 118 affects the response to oxaliplatin/5-FU combination in colon cancer. Because DNA adducts formed by cisplatin and oxaliplatin are equally well recognized by nucleotide excision repair, it is not surprising that the effect of ERCC1 activity on the cytotoxicity of cisplatin also applies to oxaliplatin (44). Nevertheless, whether this marker is a direct or an indirect predictor remains to be established. A direct measure of ERCC1 level is difficult to obtain because the experiments undertaken to define ERCC1 protein expression using immunohistochemical techniques were not judged reliably enough. Furthermore, *ERCC1* gene expression can be quantified only in fresh tumors that are handled in conditions allowing high-quality RNA isolation to perform quantitative reverse transcription-PCR. Owing to these experimental limits, the *ERCC1* codon 118 genotyping seems to be an interesting alternative that can be routinely done at a reasonable cost.

The possibility that the *ERCC1* codon 118 polymorphism is in linkage disequilibrium with another *ERCC1* mutation or polymorphism that directly affects its expression, or with another gene, cannot be ruled out. However, although genetic testing for the *ERCC1* codon 118 polymorphism would be in this case an indirect predictor, it may still represent a valuable molecular marker to predict the response of metastatic colorectal cancer to oxaliplatin treatment.

The fact that loss of heterozygosity (LOH) for nucleotide excision repair genes has been reported to occur in various sporadic carcinomas prompted us to search for LOH for the *ERCC1* gene in our colorectal cancer samples (45). Only 1 of the 41 samples analyzed displayed LOH, in keeping with results obtained in a series of patients with advanced colorectal cancer, where the only example of LOH occurred for *XRCC3*, from a total of the 149 heterozygous loci of nucleotide excision repair genes typed, which included *ERCC1*, *XPD*, *XPF*, *XPG*, *XRCC1*, and *XRCC3* (38). In the other study addressing the question of LOH of nucleotide excision repair genes in colorectal cancer, the frequency of LOH was rather low and was restricted to *XPE* and *XPB* only (45). Altogether, these data indicate that the deletion of the 19q13 chromosomal region containing the *ERCC1* gene, where numerous other genes involved in DNA repair, notably *XRCC1*, *ERCC2*, *XPD*, and *ligase I*, also map, seems to be an infrequent event in metastatic colorectal cancer and is probably not an important genetic determinant for colorectal carcinogenesis.

In conclusion, this study allowed us to establish that the *ERCC1* polymorphism at codon 118 is a useful molecular criterion to predict sensitivity of patients with metastatic colorectal cancer to oxaliplatin. Provided that our results are confirmed on larger prospective series, we propose that the *ERCC1* codon 118 polymorphism should be routinely done to avoid random selection of first-line chemotherapy and to improve the clinical management of patients with metastatic colorectal cancer by selecting those who are more likely to benefit from treatment with oxaliplatin.

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