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ORIGINAL ARTICLE

MiR-218 and miR-100 polymorphisms as markers of irinotecan-based chemotherapy response in metastatic colorectal cancer

Dimitra-Ioanna Lampropoulou[1] · Gerasimos Aravantinos[1] · Konstantinos Laschos[1] · Theodosis Theodosopoulos[2] · Christos Papadimitriou[2] · Maria Gazouli[3]

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Abstract

Purpose Colorectal cancer is the fourth cause of cancer-related death. Drug toxicity and resistance remain concerns of major importance. miR-100 and miR-218 are micro-RNAs that regulate cellular proliferation, differentiation and apoptosis acting as oncogenes and tumour suppressors; their functions and have been linked with toxicity development and drug resistance.

Methods We investigated the correlation between rs11134527 miR-218 and rs1834306 miR-100 polymorphisms and irinotecan-based regimens with regard to drug efficacy and toxicity. A total of 105 mCRC patients receiving irinotecan-based regimens were included in our study and assessed in terms of toxicity development and response to treatment. Rs11134527 miR-218 and rs1834306 miR-100 polymorphism genotyping in the peripheral blood was performed with PCR-RFLP.

Results Neither rs11134527 miR-218 nor rs1834306 miR-100 are associated with toxicity risk to treatment regimens. GA/AA genotypes of rs11134527 and CT/TT genotypes of rs1834306 were associated with a significantly reduced time-to-progression (TTP) and overall survival (OS).

Conclusions GA/AA genotypes of rs11134527 miR-218 and CT/TT genotypes of rs1834306 miR-100 polymorphisms could serve as prognostic biomarkers of TTP and OS. Carriers of the A allele of the miR-218 rs11134527 and T allele of the miR-100 rs1834306 polymorphisms are more likely not to respond to irinotecan-based therapies. However, further studies in larger patient populations are required.

Keywords miRNAs · Single-nucleotide polymorphisms · mCRC · Irinotecan · Chemotherapy

Introduction

Colorectal cancer (CRC) is the third most commonly diagnosed cancer and the fourth leading cause of cancer-related death globally [1]. Synchronous presentation of metastases upon primary diagnosis has been associated with worse prognosis compared with metachronous development of metastatic disease [2]. microRNAs (miRs) play key roles in the pathogenesis of cancer and can act both as oncogenes and tumour suppressors. There is also evidence that mi-RNA expression is associated with tumour resistance to chemotherapy in many ways [3]; on this basis, further research on the field of pharmacogenomics has suggested that several microRNA polymorphisms are involved in pathways affecting drug pharmacokinetic parameters [4]. Both miR-218 and miR-100 have been associated with drug resistance and response to treatment [3, 5–7]. However, the impact of the most known polymorphisms of these miRs on toxicity development has not been widely studied.

miR-100 is one of the most popular miRs in cancer research. However, its expression in different malignancies remains controversial, indicating both oncogenic and tumour suppressive functions [8–10]. Chen et al. reported that reduced expression of miR-100 was associated with poor prognosis in CRC patients [11]. In line with previous observations, miR-100 was recently proposed as a possible biomarker for risk assessment of lymph node metastasis in CRC [12]. Moreover, Boni et al. concluded that there may be a significant correlation between SNP rs1834306 and prolonged time

✉ Maria Gazouli
mgazouli@med.uoa.gr

[1] Second Department of Medical Oncology, General Oncology Hospital of Kifissia "Agioi Anargiroi", Athens, Greece

[2] Second Department of Surgery, Aretaieion Hospital, Medical School, National and Kapodistrian University of Athens, Athens, Greece

[3] Laboratory of Biology, Medical School, National and Kapodistrian University of Athens, Michalakopoulou 176, 11527 Athens, Greece

to progression in mCRC patients receiving regimens including 5-FU and irinotecan [13]. It has also been suggested that miR-100 is overexpressed in both intrinsic and acquired cetuximab resistance in CRC cell lines [7]; interestingly, Yang et al. reported that miR-100 may play also an important role in regulating the radiosensitivity of CRC [14].

miR-218 is a newly discovered miR with various roles in cancer tumorigenesis including cell proliferation, apoptosis and drug resistance. miR-218 downregulation has been documented in several studies indicating its role as a tumour suppressor [15, 16]. Additionally, rs11134527 variant has been implicated with the development of several types of cancer [17–20]. However, this concept has been challenged by a recent meta-analysis conducted by Moazeni-Roodi et al. where no significant association was found between miR-218 rs11134527 and cancer susceptibility in Asian populations [21]. Pavkovic et al. first reported microRNA expression changes in cisplatin-induced kidney injury in rats [22]. Furthermore, gentamycin-induced proximal tubular injury has also been associated with alterations in seven mRNAs, including miR-218 [23]. Finally, Li et al. reported that miR-218 is involved in the development of 5-FU resistance in CRC [24].

Irinotecan, an analogue of camptothecin, has been a component of chemotherapy regimens used to treat mCRC. However, it displays significant toxicity that sometimes can be life-threatening [25], indicating that personalized dosing algorithms need to be developed [26]. The backbone for mCRC treatment includes mainly oxaliplatin and irinotecan-based regimens, such as the following: FOLFOX (oxaliplatin, 5-fluorouracil and leucovorin); FOLFIRI (irinotecan, 5-fluorouracil, and leucovorin); CAPOX (capecitabine and oxaliplatin); CAPIRI (capecitabine and irinotecan); and FOLFOXIRI (infusional 5-FU/LV, oxaliplatin and irinotecan) [27]. Over the last decade, targeted therapies such as anti-VEGF (bevacizumab, aflibercept) and anti-EGFR agents (panitumumab, cetuximab) have been approved for mCRC adding in further improvements in RR, PFS and OS [28–30].

Taking these into consideration, in the present study we aimed to investigate the connection between two microRNA polymorphisms (rs11134527 miR-218 and rs1834306 miR-100) and drug resistance as well as toxicity in two Caucasian patient groups that were treated with irinotecan-based chemotherapy.

Patients and methods

Patients

Incident cases of 105 patients with histologically confirmed CRC, during the period 2005 through 2018, were recruited. The patients had no previous exposure to chemotherapy and adequate bone marrow, renal and hepatic function. All participants in the study signed an informed consent form. This case–control study is in accordance with the Helsinki Declaration and has been approved by the centres Review Board. Maximum of twelve cycles of chemotherapy were used and were administered until disease progression or until unacceptable toxicity. Additionally, only patients with performance status 0–2 (ECOG scale) were included in the study. All patients received an irinotecan-based therapy combined with aflibercept, cetuximab, bevacizumab or panitumumab, and capecitabine or 5-FU. The treatment regimens used were based on the therapeutic protocols recommended by the Hellenic Society of Medical Oncology [31]. The combination regimens were administered as previously described [32]. Regarding the efficacy evaluation of the treatment, we used the Response Evaluation Criteria in Solid Tumors (RECIST v. 1.1) as previously described [33]. The toxicity was evaluated in every chemotherapy cycle based on Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 [34]. Patient clinicopathological data are presented on Table 1.

Genotyping of miR-218 rs11134527 and miR-100 rs1834306

DNA was extracted from frozen blood samples using a DNA extraction kit (Nucleospin Blood, Macherey-Nagel, Germany), according to the manufacturer's instructions. Genotyping of miRNA polymorphisms was performed using the PCR-RFLP method as previously described [20].

Statistical analysis

Genotype and allele frequencies were compared using the χ^2 test with Yate's correction. Odds ratios (OR) and 95% confidence intervals (95% CI) were calculated with the analogous χ^2 distribution test. The p values were two tailed, and $p < 0.05$ was determined to be significant.

The survival curves were made using the Kaplan–Meier method using the log-rank test. The influence of each variable on survival was analysed by the multivariate analysis of Cox proportional hazard model. The comparisons were performed using GraphPad version 3.00 (GraphPad Software Inc., San Diego, CA, USA).

Results

A total of 105 CRC patients were included in the analysis and successfully genotyped for miR-218 (rs11134527) and miR-100 (rs1834306) polymorphisms. The allelic

Table 1 Patient characteristics and therapeutic approaches

Characteristics		Number of patients
Age (years)	Mean	69.42
	Range	43–90
Gender	Male	58
	Female	47
Surgery on primary	Yes	92
	No	13
Primary location	Colon	31
	Sigmoid	29
	Rectum	25
	Orthosigmoid	20
Metastasis site	Liver	40
	Lung	24
	Peritoneum	6
	Adrenal gland	1
	Multiple sites	34
Therapeutics	Bevacizumab, irinotecan and capecitabine	41
		12
	Panitumumab, irinotecan and capecitabine	23
		16
	Bevacizumab, irinotecan and 5-FU	6
	Panitumumab, irinotecan and 5-FU	5
	Aflibercept, irinotecan and 5-FU	2
	Cetuximab, irinotecan and 5-FU	
	Cetuximab, irinotecan and capecitabine	
Response status	Complete response (CR) + partial response (PR)	34
		36
	Stable disease (SD)	35
	Progressive disease (PD)	
Toxicity effect	Yes	80
	No	25

frequencies observed for both polymorphisms were in accordance with probability limits of Hardy–Weinberg equilibrium. Until August 2018, objective response (CR + PR) was identified in 34 (32.38%) patients, while 36 (34.29%) patients were characterized as SD and 35 (33.33%) as PD. No statistical significance was found between objective response and SD and both rs11134527 and rs1834306 genotypes. Regarding miR-218 rs11134527 polymorphism, a statistically significant correlation was detected between rs11134527 GA and AA genotypes and the PD patients' group ($p = 0.036$ and $p = 0.033$, respectively). Based on this, as illustrated in Table 2, the A allele carriers are more likely not to respond to irinotecan-based therapies ($p = 0.002$). Additionally, as indicated in Table 2, the PD patients' group was found to be statistically correlated with CT and TT genotypes of miR-100 rs1834306 polymorphism ($p = 0.038$ and 0.032 respectively). Furthermore, our results indicate that T allele does not appear to be a favourable factor regarding response in patients receiving irinotecan-based regimens ($p = 0.002$).

The most frequently treatment-related toxicities were observed in 80 out of 105 patients (76.19%) included in our study (Table 1). Our findings did not reveal any significant differences between the toxicity risk and both rs11134527 and rs1834306 genotypes. However, as indicated in Table 3, an association close to the margin of statistical significance ($p = 0.07$) was observed between the carriers of the miR-100 rs1834306 T allele and toxicity development.

Table 4 shows the association of rs11134527 and rs1834306 genotypes with overall survival. During the study period, there were 62 deaths. The survival was calculated from the date of the first treatment with irinotecan-based combinations until death from any cause. Regarding the rs11134527 GA + AA genotypes were found to be related with a significantly lower overall survival ($p = 0.04$). Additionally, the rs1834306 CT + TT genotypes were also associated with lower overall survival ($p = 0.03$) (Fig. 1). The multivariate analysis regarding survival impact of the different polymorphisms revealed that only the presence of rs1834306 CT + TT genotypes might be an independent prognostic factor predicting overall survival (HR 0.49, 95% CI 0.31–0.76, $p = 0.002$).

Discussion

Various treatment combinations including irinotecan, other chemotherapeutic drugs and recently discovered targeted cancer agents have improved survival rates in mCRC [28–30]. However, irinotecan has been associated with the development of dose-dependent toxicities, mainly due to its wide interpatient pharmacogenetic variability [25, 26]. Thus, over the past decades, research has focused on identifying genetic variants associated with irinotecan in order to develop a strategy towards individualized treatment [13, 26, 32, 35].

Many studies have also investigated the role of miRNA SNPs in cancer risk and prognosis. Li et al. reported the role of miR-218 suppression in 5-FU resistance and poorer OS and RFS in colorectal cancer patients [24]. Similarly, Hu et al. found that miR-218 was downregulated in doxorubicin- and paclitaxel-resistant breast cancer cell lines [6]. On the other hand, Zhuang et al. demonstrated that miR-218 was significantly overexpressed in resistant oral cancer cells to cisplatin [36]. To the best of our knowledge, no previous study has investigated the association between miR-218 expression or miR-218 rs11134527 and irinotecan resistance.

Polymorphisms and expression of miR-100 have been correlated with cancer development and prognosis [8–12]. However, the rs1834306 polymorphism impact on the development and prognosis of several clinical entities,

Table 2 Genotype distributions and therapeutic patient's response status (SD vs CR + PR, and PD vs CR + PR)

rs11134527	CR + PR	SD	*p*; OR (95% CI)	PD	*p*; OR (95% CI)
GG	25	23	1.00	14	1.00
GA	8	11	0.59; 1.49 (0.51–4.37)	15	0.036; 3.35 (1.14–9.85)
AA	1	2	0.61; 2.17 (1.18–25.62)	6	0.033; 10.71 (1.17–98.29)
G allele	58	57	1.00	43	1.00
A allele	10	15	0.38; 1.53 (0.63–3.68)	27	0.002; 3.64 (1.59–8.32)
rs1834306					
CC	24	31	1.00	13	1.00
CT	9	4	0.13; 0.34 (0.09–1.25)	16	0.038; 3.28 (1.13–9.47)
TT	1	1	1.00; 0.77 (0.05–13.03)	6	0.032; 11.07 (1.20–102.25)
C allele	57	66	1.00	42	1.00
T allele	11	6	0.19; 0.47 (0.16–1.36)	28	0.002; 3.45 (1.56–7.71)

including cancer, remains controversial. For instance, miR-100 rs1834306 T>C polymorphism has been associated with a significant decreased risk of oesophageal squamous cell carcinoma [37], whereas a recent study showed that TC genotype and T allele is associated with elevated miR-100 expression and increased viral load in HBV patients [38]. Moreover, Boni et al. has linked C>T rs1834306 SNP with a significantly longer time to progression in mCRC patients treated with 5-FU and irinotecan [13].

Taken these into consideration, we investigated the correlation between germline polymorphisms in miR-218 and miR-100 and response to irinotecan-based regimens in 105 patients with incurable mCRC. More specifically, our study focused on the impact of rs11134527 miR-218 and rs1834306 miR-100 SNPs on clinical response, overall survival and toxicity development in patients receiving irinotecan-based schemes. There is evidence suggesting that the presence of allele A (AA and GA genotypes) is associated with decreased expression of mature miR-218 [39]. Moreover, as already mentioned, downregulation of miR-218 has been correlated with resistance and poor response in 5-FU-based schemes in CRC, via the activation of NF-κB/TS signalling pathway [24]. In line with these observations, we found that miR-218 rs11134527 GA and AA genotypes were significantly correlated with disease progression, suggesting that the functional impact of the variant A allele in rs11134527 may lead to poor responses in mCRC patients treated with irinotecan-based regimens. Moreover, Scartozzi et al. have already suggested a possible resistance mechanism in irinotecan-refractory mCRC patients, implicating NF-κB activation [40]. Based on the above, we could propose that the underlying mechanism of miR-218-mediated irinotecan resistance may include the regulation of NF-κB signalling pathway. To date, this is the first study to have found this correlation; however, further research should be carried out in order to validate our results and hypothesis of the proposed irinotecan resistance mechanism.

Regarding the second polymorphism of our study, miR-100 rs1834306, we found that CT/TT genotypes were statistically correlated with poor responses. Boni et al. have found that mCRC patients harbouring C allele (CC/CT genotypes) presented a longer time to progression when treated with regimens including 5-FU and irinotecan

Table 3 Genotype distributions and toxicity

rs11134527	Yes	No	*p*; OR (95% CI)
GG	45	17	1.00
GA	27	7	0.62; 1.46 (0.53–3.97)
AA	8	1	0.43; 3.02 (0.35–26.02)
G allele	117	41	1.00
A allele	43	9	0.26; 1.67 (0.75–3.73)
rs1834306			
CC	49	19	1.00
CT	23	6	0.61; 1.49 (0.52–4.22)
TT	8	0	0.19; 6.69 (0.37–121.8)
C allele	121	44	1.00
T allele	39	6	0.07; 2.36 (0.93–5.97)

Table 4 Rs11134527 and rs1834306 genotypes in association with overall survival

Genotype	Overall survival			
	Events (*n*)	13-year survival (%)[a]	Hazard ratio (95% CI)	*p*
rs11134527				
GG	30	60.62	1.00 (Reference)	
GA + AA	32	50.74	1.37 (0.83–2.26)	0.04
rs1834306				
CC	29	60.74	1.00 (Reference)	
CT + TT	33	49.62	1.66 (1.01–2.73)	0.03

[a] Proportion of survival derived from Kaplan–Meier analysis

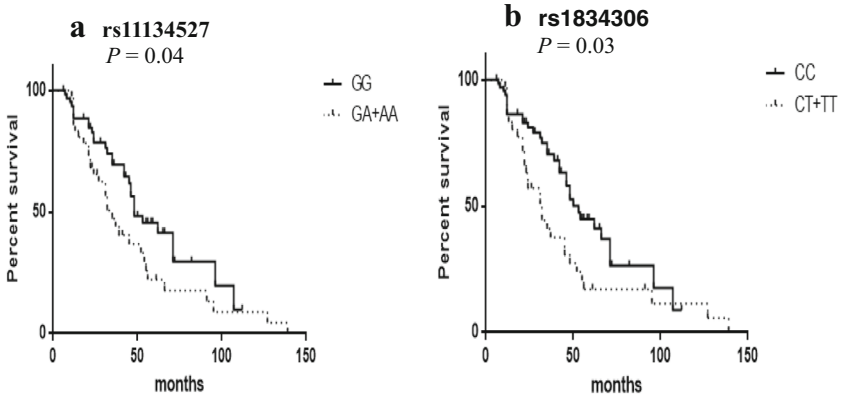

Fig. 1 Association of overall survival with genotypes of miR-218 rs11134527 (**a**) and miR-100 rs1834306 (**b**) polymorphisms. Kaplan–Meier curve represents the percentage of survival in months of patient's different genotypes

[13]. Our results confirm previous findings, indicating that the variant T allele of rs1834306 may be an unfavourable factor regarding PFS in mCRC patients treated with irinotecan-based regimens.

Based on our data, miR-218 rs11134527 GA/AA genotypes are also associated with lower overall survival. Taken together, this finding and our concurrent results that correlate GA/AA genotypes with disease progression suggest that the presence of A allele is potentially a risk factor regarding the prognosis (PFS and OS) of mCRC patients receiving irinotecan-based schemes. Previous studies have demonstrated that the presence of G allele in rs11134527 pri-miR-218 region is associated with increased expression of mature miR-218 [39]. Our observations are in agreement with Jiang et al.'s report that GG genotypes were associated with an increased survival rate in patients with oesophageal squamous cell carcinoma when compared with AA/AG genotypes [17].

Similarly, our analysis revealed that miR-100 rs1834306 CT/TT genotypes are related with shorter overall survival. On the contrary, Wu et al. found no significant correlation between miR-100 rs1834306 variants and overall survival in patients in advanced oesophageal cancer patients receiving platinum-based chemotherapy [41]. Furthermore, Chen et al. observed that miR-182/miR-100 ratio is implicated in survival prediction in patients with bladder cancer [42], whereas the results from a large translational study showed no significant association between rs1834306 and overall survival in patients with advanced gastric cancer [43]. These discrepancies may be attributed to the fact that miR-100 can act as both a tumour suppressor and oncogene depending on the type of cancer. Notably, despite that miR-100 has been extensively studied over the past decade, the majority of research has reported time-to-progression, and overall response but not overall survival data. Finally, as already mentioned, the impact of the SNPs under study on toxicity development has not been widely studied. However, in line with previous research, our analysis did not identify any significant associations between both miR-218 rs11134527 and miR-100 rs1834306 and toxicity development [41].

To sum up, our results need to be confirmed in future studies, especially since the functional effect and the underlying mechanisms of the miRNA SNPs in cancer pathogenesis, prognosis and toxicity development remain unknown and need further investigation. We should also reckon that the miRNA polymorphisms may interact in a multifactorial level with the complex regimens that are currently used to treat mCRC patients, such as the ones used in our study population. Therefore, apart from the discovery of novel biomarkers, further larger scale, multi-level research should be carried out in order to validate our results and better understand both the response and toxicity incidence in mCRC patients treated with irinotecan-based regimens.

Conclusions

In conclusion, our study provides the first evidence of the association between both miR-218 rs11134527 and miR-100 rs1834306 polymorphism and response in mCRC patients treated with irinotecan-based regimens. Additionally, gene expression profiling analysis revealed that carriers of the mutated A allele of miR-218 rs11134527 and carriers of the mutated T allele of miR-100 rs1834306 are more likely not to respond to irinotecan-based schemes. Finally, rs11134527 GA/AA genotypes and rs1834306 CT/TT genotypes were found to be related with a significantly lower overall survival.

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Compliance with ethical standards

All participants in the study signed an informed consent form. This case–control study is in accordance with the Helsinki Declaration and has been approved by the centres Review Board

Conflict of interest The authors declare that they have no conflict of interests.

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