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Gastrointestinal perforation associated with bevacizumab use in metastatic colorectal cancer: Results from a large treatment observational cohort study

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Abstract ***Background:*** Bevacizumab prolongs overall and progression-free survival when added to fluorouracil-based chemotherapy in patients with metastatic colorectal cancer in randomised controlled trials (RCTs). However, gastrointestinal perforation (GIP) occurs in 1–2% of treated patients. We sought to describe the incidence, temporal pattern, outcomes and potential risk factors for GIP in a large, community-based observational cohort study of patients treated with bevacizumab.

Patients and methods: Baseline patient and tumour characteristics, including potential GIP risk factors, were collected at study entry. Treatment, targeted adverse events, progression events and survival data were recorded every 3 months. Detailed clinical information was collected for all patients experiencing a GIP event. Effects of baseline risk factors on GIP risk were investigated using Cox proportional hazards regression.

Results: Of 1953 evaluable patients followed for a median of 20.1 months, 37 (1.9%) experienced GIP. Most GIP events were surgically managed with successful outcomes; four events were fatal. The majority of GIP events (26/37) occurred $\leqslant$6 months after starting bevacizumab (median, 3.35 months). Univariate and multivariate analyses showed that age $\geqslant$65 years was significantly associated with lower GIP risk. In multivariate analyses, intact primary tumour

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and prior adjuvant radiotherapy were significantly associated with increased risk of GIP within 6 months after starting bevacizumab. A regression analysis that assessed the risk of GIP over time showed no cumulative risk associated with bevacizumab exposure.

Conclusion: The observed rate of GIP in this large, community-based experience was consistent with rates reported in RCTs. Most events were successfully managed with surgical intervention.

1. Introduction

Bevacizumab (Avastin®, Genentech, Inc., South San Francisco, CA), a recombinant humanised monoclonal antibody targeting vascular endothelial growth factor, is an antiangiogenic agent approved for the treatment of multiple solid tumours. In the first- and second-line treatment of metastatic colorectal cancer (mCRC), bevacizumab prolonged overall survival (OS) and progression-free survival when combined with fluorouracil (FU)-based chemotherapy regimens.[1–3] In two phase 3 trials of bevacizumab in mCRC, gastrointestinal perforation (GIP) was an uncommon but serious adverse event occurring at rates of 1.5% and 1.1%.[1,3]

Because GIP events in these randomised controlled trials (RCTs) were infrequent and patient follow-up was not longitudinal, the risk of experiencing a GIP over time with bevacizumab exposure and the contribution of potential risk factors are not well characterised. Moreover, patients selected for clinical trials likely differ from the general population of patients with mCRC.

BRiTE (Bevacizumab Regimens' Investigation of Treatment Effects), a prospective, observational cohort study (OCS) initiated when the US Food and Drug Administration approved bevacizumab for the first-line treatment of mCRC, was designed to explore clinical outcomes with bevacizumab-based therapy in a community or 'real-world' cohort of patients, including the incidence, clinical course and potential risk factors associated with uncommon but serious adverse events, such as GIP. Baseline patient characteristics and clinical outcomes in BRiTE have been published previously.[4,5] Here we report a protocol-specified analysis that examined risk factors and long-term outcomes associated with GIP in BRiTE, including analyses of timing and potential associations with known risk factors.

2. Patients and methods

2.1. Study design and patients

Details of the study design were reported previously.[4,5] In brief, this prospective OCS followed patients with metastatic or locally advanced and unresectable colorectal cancer receiving bevacizumab with initial chemotherapy. No other eligibility requirements were specified. Chemotherapy regimens, dose, duration of bevacizumab treatment and any tumour assessments were at the physician's discretion.

2.2. Data collection

Patient data were recorded at baseline and then quarterly until study completion, patient death, withdrawal of consent, loss to follow-up or study data cutoff (15th October 2008), whichever occurred first. Prespecified potential baseline risk factors for GIP, including intact primary tumour, sigmoidoscopy or colonoscopy within 1 month preceding the start of bevacizumab administration, recent major surgery, prior adjuvant radiotherapy, chronic use of aspirin or other non-steroidal anti-inflammatory drugs (NSAIDs) and a history of peptic ulcer disease or diverticulosis were recorded. At follow-up, sites were required to answer the following question with a 'yes' or 'no': Has the patient experienced a GIP event? If the response was 'yes', information on the event onset and resolution dates, suspected cause, change in bevacizumab treatment and additional GIP risk factors were collected. Potential GIP events, based on Common Terminology Criteria for Adverse Events (v. 3.0),[6] were reviewed clinically to ensure identification of all events and to distinguish multiple events from the continuation of a single event.

2.3. Statistical analysis

All patients who received at least one dose of bevacizumab and for whom safety data were collected were included in the analysis. Baseline patient and disease characteristics were summarised using descriptive statistics. The number and corresponding rate of GIP events were determined for the overall BRiTE sample and for patients with predisposing risk factors at baseline.

The effects of baseline risk factors on the length of time to first GIP event were investigated using Cox proportional hazards regression. Patients without a GIP event were censored at the time of death, study discontinuation, study data cutoff or 90 days after receiving the last bevacizumab dose, whichever occurred first. Risk factors examined included Eastern Cooperative Oncology Group (ECOG) performance status, age, chronic aspirin (>325 mg) or NSAID therapy, peptic ulcer disease requiring medication, known diverticulosis, intact primary tumour, sigmoidoscopy or colonoscopy

within 1 month before starting bevacizumab treatment, prior adjuvant radiotherapy, primary tumour location and timing of prior major surgery. Univariate and multivariate proportional hazards models were fit for time to first GIP for all GIP events and separately for events occurring $\leqslant$6 months and >6 months after starting bevacizumab. Separate univariate proportional hazards regression models were fit for each binary covariate. Covariates with a p-value $\leqslant$0.3 for the likelihood ratio test of the null hypothesis that the covariate regression coefficient is zero were entered into an initial multivariate model. From this initial multivariate model, covariates were sequentially removed based on p-value of the likelihood ratio test of the null hypothesis for each regression coefficient, until all covariates remaining in the final model had a p-value $\leqslant$0.3 for removal. This process of backward stepwise elimination was used to reduce potential confounding. Hazard ratios (HRs) and 95% confidence intervals (CI) from the proportional hazards regression analysis are reported for risk factors included in the final model. Additional analyses using p-value $\leqslant$0.1 criterion for covariate selection were also conducted.

The risk of GIP as a function of time since bevacizumab initiation is summarised graphically. For each month, GIP risk was computed as the ratio of the number of events over the number of patients at risk at month start. Monthly risks were smoothed using a cubic B-spline smoother with uniformly spaced knots and empirically chosen degrees of freedom and plotted with 95% confidence bounds. Analyses were conducted using SAS System for Open VMS, v. 8.2, and, for multivariate analyses, SAS System for Windows, v. 9.2 (SAS Institute, Cary, NC).

2.4. Ethics

BRiTE was conducted according to the International Conference on Harmonisation E6 Guideline for Good Clinical Practice and in compliance with US requirements, including the Health Insurance Portability and Accountability Act. Patients provided signed informed consent and authorisation for study participation.

3. Results

Of 1967 patients enroled at 248 study sites (primarily community-based; nine were academic research centres) in 49 states between February 2004 and June 2005, 1953 (99.2%) were evaluable. Fifteen non-evaluable patients did not receive bevacizumab during first-line therapy. Median follow-up was 20.1 months (range, 0.07–51.2 months). Baseline demographic and disease characteristics are reported elsewhere.[4,5] The most common chemotherapy regimens combined with bevacizumab were FOLFOX (oxaliplatin, infusional FU/leucovorin; 55.9%), FOLFIRI (irinotecan, infusional FU/leucovorin; 14.3%) and IFL (irinotecan, bolus FU/leucovorin; 9.7%).

Thirty-seven GIP events were reported in 1953 patients (1.9%). Table 1 presents the number and percentage of evaluable patients with GIP events by baseline characteristics considered to be potential univariate risk factors for GIP. The only significant risk factor (i.e. HR substantially different from the reference value of 1.0, with a non-overlapping 95% CI) identified by univariate analysis was patient age. Older patients ($\geqslant$65 years) had a reduced risk of experiencing a GIP event. Risk factors associated with a HR greater than 1.0 (but not statistically significant) were intact primary tumour, rectum as the site of the primary tumour, sigmoidoscopy or colonoscopy $\leqslant$1 month before starting bevacizumab and prior adjuvant radiotherapy. No difference in GIP risk was noted in the 278 patients undergoing major surgery within 30 days before starting bevacizumab therapy (HR 0.33, 95% CI 0.08–1.39). In addition, GIP risk was examined by first-line chemotherapy regimen, and there were no apparent differences in the proportion of patients experiencing GIP by regimen (FOLFOX, 21/1092 [1.9%]; FOLFIRI, 6/280 [2.1%]; IFL, 2/132 [1.5%], XELOX [capecitabine and oxaliplatin], 1/94 [1.1%]; 'other' chemotherapy, 1/166 [0.6%]). Relative to patients receiving FOLFOX or XELOX, those receiving FOLFIRI had an HR of 1.12 (95% CI 0.46–2.7) and those receiving other regimens had an HR of 1.05 (95% CI 0.48–2.28).

Characteristics of the 37 patients with a GIP event are summarised in Appendix A. GIP most commonly occurred within 6 months of starting bevacizumab therapy (26; 70.2%); six patients experienced a GIP event more than 8 months after bevacizumab initiation. Accounting for the number of patients at risk, there was an initial decline in the smoothed GIP risk over time on bevacizumab, which remained level through 3 years (Fig. 1). Median time to a GIP event was 3.35 months (range, 0.39–37.32 months).

Most GIP events were surgically managed with satisfactory outcomes. GIP events were fatal in four patients (10.8%), all of whom experienced GIP within 6 months of initiating bevacizumab (range, 0.49–4.37 months).

Separate multivariate analyses were performed according to the timing of GIP events relative to the start of bevacizumab (any time, $\leqslant$6 months, >6 months). In the analysis of all events, age, intact primary tumour, prior adjuvant radiotherapy and major surgery $\leqslant$30 days before starting bevacizumab were retained in the final model (Table 2). Within the multivariate model, patients $\geqslant$65 years at baseline had a significantly lower GIP risk than patients <65 years (HR = 0.48; 95% CI 0.23–1.00). Intact primary tumour and prior adjuvant radiotherapy each approximately doubled the hazard for GIP, with a trend towards

Table 1
Number (%) of patients with gastrointestinal perforation events by baseline risk factor levels and corresponding univariate HRs.

Baseline risk factor level (total patients)	Patients with GIP event (%)	Univariate HR (95% confidence intervals (CI))
ECOG performance status		
0 ($n = 837$)	18 (2.2)	1.0 (reference)
$\geqslant 1$ ($n = 961$)	17 (1.8)	0.94 (0.48–1.82)
Unknown ($n = 155$)	2 (1.3)	0.63 (0.15–2.71)
Age group (years)		
<65 ($n = 1057$)	27 (2.6)	1.0 (reference)
$\geqslant 65$ ($n = 896$)	10 (1.1)	0.47 (0.23–0.98)
Chronic use of aspirin (>325 mg/day) or other NSAID		
No ($n = 1920$)	37 (1.9)	1.0 (reference)
Yes ($n = 33$)	0 (0.0)	0.00 (0.00–NE)
Peptic ulcer disease requiring medication		
No ($n = 1896$)	36 (1.9)	1.0 (reference)
Yes ($n = 57$)	1 (1.8)	1.02 (0.14–7.44)
Known diverticulosis		
No ($n = 1837$)	35 (1.9)	1.0 (reference)
Yes (n = 116)	2 (1.7)	0.97 (0.23–4.04)
Intact primary tumour		
No (n = 1649)	28 (1.7)	1.0 (reference)
Yes (n = 304)	9 (3.0)	1.94 (0.91–4.12)
Site of primary tumour		
Colon (n = 1551)	26 (1.7)	1.0 (reference)
Rectum (n = 399)	11 (2.8)	1.61 (0.79–3.26)
Sigmoidoscopy or colonoscopy $\leqslant$1 month before starting bevacizumab		
No ($n = 1682$)	30 (1.8)	1.0 (reference)
Yes ($n = 271$)	7 (2.6)	1.45 (0.64–3.31)
Prior adjuvant radiotherapy		
No ($n = 1688$)	28 (1.7)	1.0 (reference)
Yes ($n = 262$)	9 (3.4)	2.11 (0.99–4.46)
Major surgery $\leqslant$30 days before starting bevacizumab		
No ($n = 1675$)	35 (2.1)	1.0 (reference)
Yes ($n = 278$)	2 (0.7)	0.33 (0.08–1.39)

ECOG: Eastern Cooperative Oncology Group; GIP: gastrointestinal perforation; HR: hazard ratio; NE: not evaluable; NSAID: non-steroidal anti-inflammatory drug.

statistical significance, although the absolute risk of GIP remained low for these patients (3.0% and 3.4%, respectively). Alternative analyses using $p \leqslant 0.1$ criterion for covariate selection resulted in a similar multivariate model. For the subset of patients having GIP events within 6 months of starting bevacizumab, major surgery within the preceding 30 days did not satisfy the $p \leqslant 0.3$ criterion and was not retained in the final model. Both intact primary tumour (HR = 2.72; 95% CI 1.17–6.32) and prior adjuvant radiotherapy (HR = 2.60; 95% 1.08–6.25) were statistically significant ($p < 0.05$) risk factors for a GIP event occurring within this timeframe. In the subset of patients having GIP events with an onset >6 months after starting bevacizumab, only prior adjuvant radiotherapy and rectal primary tumour site were retained in the final model, but neither reached statistical significance.

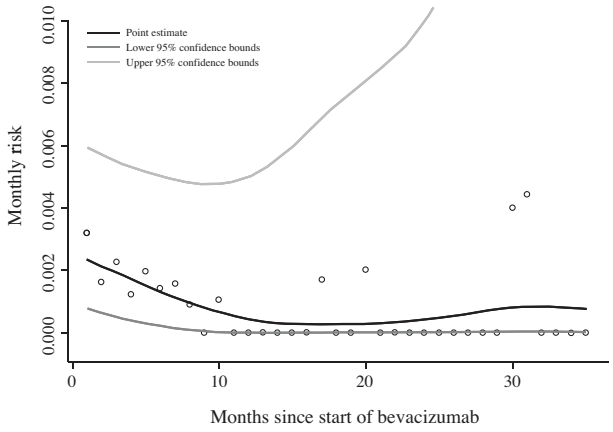

Fig. 1. Risk of a gastrointestinal perforation event as a function of time since the start of treatment with bevacizumab.

4. Discussion

The magnitude of the risk of GIP, an uncommon but potentially serious adverse event associated with bevacizumab therapy, is uncertain because data from RCTs were inadequate to provide precise estimates. Clinical or autopsy evidence to confirm proposed pathophysiologic mechanisms underlying this association (e.g. bevacizumab-induced local ischaemia due to inadequate vascular perfusion of GI tissue[7,8] and/or compromised vascular integrity due to a disturbance in endothelial cell and platelet interaction[9]) is lacking, and contributing risk factors are poorly understood.

Originally noted in CRC, GIP has also been observed with bevacizumab use in lung,[10] renal,[11] pancreatic,[12,13] breast,[14] and ovarian tumours.[15] A recent meta-analysis of 17 RCTs evaluating bevacizumab-containing regimens across a number of malignancies, which did not adjust for treatment patterns, chemotherapy choices, or baseline patient and tumour characteristics, reported that bevacizumab treatment was associated with a 0.9% incidence of GIP and an approximately twofold increase in risk relative to the control (2.14; 95% CI 1.19–3.85).[16] However, intra-abdominal tumours, including colorectal, ovarian, pancreatic, and renal cell cancers, appear to be associated with a higher incidence of GIP than malignancies such as lung, breast and glioblastoma. With the exception of a phase 2 trial in heavily pretreated patients with advanced ovarian cancer that was halted because of an unexpectedly high GIP rate, data from RCTs have suggested that patients with CRC may be the most likely to experience bevacizumab-associated GIP, with an overall incidence of $\leqslant$2%. The relative risk of GIP among patients with CRC receiving bevacizumab, based on pooled, unadjusted data from RCTs, was calculated as 3.10 (95% CI 1.26–7.63), including a relative risk of 3.68 (95% CI 1.28–10.63) in those with metastatic disease.[16] The risk of GIP in patients with CRC may be enhanced because of

predisposing GI toxicity (e.g. bowel inflammation) from chemotherapy regimens[17,18] and/or pelvic radiation, or, in patients with an intact tumour, and because of bevacizumab-induced changes in the tumour vasculature, including possible generation of microemboli.[17,19] Notably, the phase 2 NSABP (National Surgical Adjuvant Breast and Bowel Project) C-10 study of mFOLFOX6 + bevacizumab in mCRC patients with an intact primary tumour,[20] as well as the phase 3 NSABP C-08 and AVANT (**Ava**stin® in adjuva**nt** colon cancer) studies of adjuvant FOLFOX or XELOX ± bevacizumab in stage II or III colon cancer,[21,22] showed low rates of GIP in bevacizumab-treated patients.

As a complement to the RCT data, the present study evaluated GIP incidence and the effect of potential risk factors for GIP in a large, community-based, prospective cohort of patients with metastatic or locally advanced CRC who were receiving bevacizumab combined with first-line chemotherapy. The overall incidence of GIP events (1.9%) observed in this 'real-life' setting, with a median follow-up of 20.1 months, is similar to that reported in phase 3 RCTs of bevacizumab combined with FU-based chemotherapy for mCRC.[1,3] Given that patients in the BRiTE OCS are, on average, older with a poorer ECOG performance status at baseline than patients in the mCRC RCTs, it is reassuring that there is currently no evidence of a greater risk for GIP in this patient cohort. In addition, several events reported by study sites as GIP (e.g. GI bleeding, radiation enteritis, and GI fistula) may have been misclassified, potentially contributing to an overestimation of the incidence of GIPs in BRiTE.

The evaluation of risk factors for GIP with bevacizumab use revealed that patients with an intact primary tumour, history of adjuvant radiotherapy, or age <65 years were at an increased risk for subsequent GIP events. Intact primary tumour and prior adjuvant radiotherapy were significant risk factors for GIP events occurring within 6 months of starting bevacizumab, whereas age <65 years was associated with a higher risk of GIP at any time after starting bevacizumab according to multivariate analyses. These findings are consistent with those of an analysis of GIP events in a similar study of an international cohort of patients with mCRC receiving bevacizumab with first-line chemotherapy (First BEAT [Bevacizumab Expanded Access Trial]).[23] Multivariate analyses from BRiTE showed that ECOG performance status (0 versus ⩾1), site of primary tumour (colon versus rectum), and sigmoidoscopy or colonoscopy within 1 month before starting bevacizumab (yes versus no) had no association with GIP risk. Additionally, the risk for GIP was not increased with the use of any specific chemotherapy regimen. Our analyses also suggest that major surgery ⩽30 days before starting bevacizumab did not increase the risk of GIP; this finding is novel, as patients who had had major surgery within this timeframe were excluded from the pivotal RCTs of bevacizumab in mCRC.

Table 2
Results of multivariate Cox proportional hazards regression analyses of baseline risk factors for gastrointestinal perforation events by timing of event onset.[a]

Baseline characteristic	All GIP events		GIP onset ⩽6 months after starting BV		GIP onset >6 months after starting BV	
	HR (95 % CI)	*p* value[c]	HR (95 % CI)	*p* value[c]	HR (95 % CI)	*p* value[c]
Age group (years)						
<65	1.0 (reference)[b]		1.0 (reference)[b]		Not included[d]	–
⩾65	0.48 (0.23–1.00)	0.0500	0.47 (0.20–1.11)	0.0846		
Intact primary tumour						
No	1.0 (reference)[b]		1.0 (reference)[b]		Not included[d]	–
Yes	1.95 (0.91–4.17)	0.0874	2.72 (1.17–6.32)	0.0197		
Prior adjuvant radiotherapy						
No	1.0 (reference)[b]		1.0 (reference)[b]		1.0 (reference)[b]	
Yes	2.04 (0.95–4.38)	0.0682	2.60 (1.08–6.25)	0.0324	3.45 (0.6–19.33)	0.1595
Site of primary tumour						
Colon	Not included[d]	–	Not included[d]	–	1.0 (reference)[b]	
Rectum					0.19 (0.02–1.91)	0.1580
Major surgery ⩽30 days before starting BV						
No	1.0 (reference)[b]		Not included[d]	–	Not included[d]	–
Yes	0.38 (0.09–1.61)	0.1914				

BV, bevacizumab; CI, confidence interval; GIP, gastrointestinal perforation; HR, hazard ratio.

[a] Table presents results for risk factors selected for inclusion in at least one of the final models. Additional risk factors evaluated but not selected for final models: Eastern Cooperative Oncology Group performance status, chronic aspirin (>325 mg/day) or non-steroidal anti-inflammatory drug therapy; peptic ulcer disease requiring medication, known diverticulosis, prior sigmoidoscopy or colonoscopy ⩽1 month before starting bevacizumab; site of primary tumour. These risk factors were eliminated during backward selection process.

[b] Reference value for calculation of hazard ratio = 1.0.

[c] Backward elimination with criterion $p \leqslant 0.3$ was used to select risk factors included in final model.

[d] Covariate was not included in the proportional hazards model.

Limitations of the present analysis include the lack of a control group and the possibility of unknown or unmeasured confounding factors, such as cohort heterogeneity.

Although older patients in the general population are at risk for hospitalisation due to GI bleeding, which increases with each 5-year increment over 65 years of age,[24] BRiTE patients ⩾65 years were found to have a lower risk of GIP than patients <65 years. Data from pivotal studies have also indicated that advanced age is not associated with a greater risk of GIP.[25] In BRiTE, patients younger than 65 years did not have a greater tumour burden than older patients (based on number or size of tumours or presence of an intact primary tumour), and, on average, their ECOG performance status scores were not higher. Patient age also had no apparent association with GIP-related mortality; of the four patients with a fatal GIP event, two were in their early 50s and two were in their mid-70s.

Our finding that the majority of GIP events occur within 6 months of starting bevacizumab (median time to event = 3.35 months) is consistent with the data from RCTs and other investigations. Badgwell and colleagues reported a median time to event of 71 days (2.54 months) in a case series of 1442 patients with diverse cancer types who were treated with bevacizumab and experienced GIP events.[26] The absence of a clear increase in GIP risk over time is an important insight from longitudinal follow-up in BRiTE, particularly because evidence suggests that continuing bevacizumab beyond disease progression may improve OS.[4,27] Indeed, clinical practice may evolve to the use of more extended durations of bevacizumab exposure. In BRiTE, the three statistically significant risk factors for GIP events that were identified in either the overall analysis or the analysis of patients with GIP within 6 months after starting bevacizumab (intact primary, prior adjuvant radiotherapy, age <65 years) were not significant in patients whose GIP occurred beyond 6 months. This difference is intriguing but may reflect the smaller number of patients in the latter group.

In conclusion, in the BRiTE prospective OCS the frequency of GIP events occurring with bevacizumab combined with first-line chemotherapy in a large, community-based mCRC population was 1.9% (37/1953), which is similar to the rates in the phase 3 RCTs and to that in a large case series of patients with CRC (1.3%; 6/478).[1,3,26] Novel findings of our analysis include the lack of an association between GIP and recent major surgery before starting bevacizumab and the evidence that the risk of GIP declined during the first several months of bevacizumab therapy and then remained level through 3 years. Bevacizumab-containing therapies improve survival in patients with many common metastatic tumours; our findings should help physicians assess bevacizumab-associated risk for more serious adverse events, such as GIP, when making treatment decisions for their individual patients.

Role of the funding source

Genentech, Inc., sponsored the BRiTE trial; however, neither participating physicians nor patients were paid, and no drug was supplied. Sites were paid only for data entry. Genentech personnel participated in study design; the analysis and interpretation of data; the writing of the report and the decision to submit the report for publication.

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Conflict of interest statement

The authors have indicated the following conflicts of interests—FK and MK (consultancy, speakers bureaus for Genentech, Inc. and F. Hoffman-La Roche); PF (speakers bureaus for Genentech, Inc.); M.A., A.S. and C.B. (employees of Genentech, Inc.); AG (institution has received grants from Genentech, Inc., Daiichi, and Bayer).

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.ejca.2012.02.052.

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