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REVIEW

Management of adverse events from the treatment of encorafenib plus cetuximab for patients with *BRAF* V600E-mutant metastatic colorectal cancer: insights from the BEACON CRC study

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Colorectal cancer is the second leading cause of cancer deaths worldwide, with a 5-year relative survival of 14% in patients with metastatic colorectal cancer (mCRC). Patients with *BRAF* V600E mutations, which occur in ∼10%-15% of patients with mCRC, have a poorer prognosis compared with those with wild-type BRAF tumours. The combination of the BRAF inhibitor encorafenib with the epidermal growth factor receptor inhibitor cetuximab currently represents the only chemotherapy-free targeted therapy approved in the USA and Europe for previously treated patients with *BRAF* V600E-mutated mCRC. As a class, BRAF inhibitors are associated with dermatologic, gastrointestinal, and renal events, as well as pyrexia and secondary skin malignancies. Adverse event (AE) profiles of specific BRAF inhibitors vary, however, and are affected by the specific agents given in combination. In patients with mCRC, commonly reported AEs of cetuximab monotherapy include infusion reactions and dermatologic toxicities. Data from the phase III BEACON CRC study indicate that the combination of encorafenib with cetuximab has a distinct safety profile. Here we review the most frequently reported AEs that occurred with this combination in BEACON CRC and best practices for managing and mitigating AEs that require more than standard supportive care.

Key words: encorafenib, cetuximab, CRC, metastatic colorectal cancer, adverse events

INTRODUCTION

Colorectal cancer is the second leading cause of cancer deaths worldwide, and the 5-year relative survival for patients with metastatic disease is 14%.[1,2] The *BRAF* V600E mutation occurs in ∼10%-15% of patients with treatable metastatic colorectal cancer (mCRC).[2-11] Patients with *BRAF* V600E-mutant mCRC have a poorer prognosis compared with those with wild-type *BRAF* tumours.[12] The combination of encorafenib, a BRAF inhibitor, with cetuximab, an epidermal growth factor receptor (EGFR) inhibitor, is licensed in the USA and Europe for the treatment of previously treated adults with mCRC who have a *BRAF* V600E mutation.[13,14] The combination is included in clinical recommendations for the management of advanced mCRC that is *BRAF* V600E-mutation positive.[15] This regimen represents the only chemotherapy-free targeted therapy approved in the USA and Europe specifically indicated for previously treated patients with *BRAF* V600E-mutated mCRC. Approval was based on the results of the phase III BEACON CRC study (NCT02928224), which investigated the efficacy and safety of encorafenib plus cetuximab with or without binimetinib, a mitogen activated protein kinase kinase (MEK) inhibitor, compared with investigators' choice of irinotecan plus cetuximab or FOLFIRI (5-fluorouracil, leucovorin, and irinotecan) plus cetuximab (control) in patients with previously treated *BRAF* V600E-mutated mCRC.[16,17] In the BEACON CRC study, encorafenib plus cetuximab demonstrated significantly longer median overall survival (9.3 versus 5.9 months; hazard ratio 0.61; 95% confidence interval 0.48-0.77) and a higher objective response rate (19.5% versus 1.8%) compared with

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control.[17,18] The rate of adverse events (AEs) of grade 3 or higher was slightly greater in the control group than in the combination group; there were few treatment discontinuations (≤9%) due to AEs.[16,17]

The safety profile of cetuximab is well characterised and generally related to its mechanism of action on EGFR.[19,20] Commonly reported AEs with cetuximab monotherapy in patients with mCRC include infusion reactions (any grade: 8.4%; grade 3/4: 2.2%) and dermatologic toxicities (9.7%), which may require dosage adjustment.[19,20] As a class, BRAF inhibitors have been associated with a range of AEs including dermatologic, gastrointestinal and renal events, as well as pyrexia and secondary skin malignancies.[21,22] Individual BRAF inhibitors vary in their AE profiles, however, which is also affected by the specific agents given in combination.[21,22]

Data from the BEACON CRC study indicated that the combination of encorafenib with cetuximab has a distinct safety profile that differs from that of the previous standard of care in this setting. As such, a better understanding of AEs associated with this regimen in patients with mCRC is needed to guide clinical care. This report focuses on the most frequently reported AEs that occurred with encorafenib plus cetuximab during the BEACON CRC study (August 2019 data cut-off)[18] and on best practices for managing and mitigating those events requiring more than standard supportive care.

Background to the BEACON CRC study

Full details of the BEACON CRC study design and efficacy results have previously been reported.[16,17] Briefly, patients with *BRAF* V600E-mutated mCRC, Eastern Cooperative Oncology Group performance status of 0 or 1, and disease progression after one or two prior regimens were randomised 1 : 1 : 1 to receive encorafenib plus cetuximab and binimetinib; encorafenib plus cetuximab; or control (investigators' choice of irinotecan plus cetuximab or FOLFIRI plus cetuximab).[16,17]

Safety and tolerability were secondary endpoints and were monitored based on the incidence and severity of AEs assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03 and on the evaluation of laboratory parameters. Dermatologic examinations were carried out during screening in all groups. In the experimental, encorafenib-containing treatment groups, additional dermatologic examinations were carried out during the study: every 8 weeks from cycle 1, day 1 (i.e. on day 1 of cycles 3, 5, 7, etc.). These on-study dermatologic examinations were not carried out in the control group. All patients who received at least one dose of any study drug and at least one post-baseline safety assessment were included in the safety analysis. The BEACON CRC protocol permitted dosage adjustment and/or interruption of study drug(s).

Study population and duration of therapy

In total, 665 patients were randomised to encorafenib plus binimetinib and cetuximab ($n = 224$), encorafenib plus cetuximab ($n = 220$), or control ($n = 221$); baseline characteristics were generally similar across study groups (Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2021.100328).[16,17,23] The median duration of exposure to study drug was 2.7-fold longer for patients receiving encorafenib plus cetuximab compared with patients in the control group (19 versus 7 weeks; Table 1).

Overview of AEs and laboratory abnormalities with encorafenib plus cetuximab

The overall incidence of AEs, serious AEs, and AEs leading to discontinuation was similar across the three treatment groups (Table 1). The most frequently reported any-cause AEs (any grade and grade ≥3) and select laboratory abnormalities with encorafenib plus cetuximab are shown in Table 2. The most commonly reported AEs of any grade with encorafenib plus cetuximab were gastrointestinal [diarrhoea

Table 1. Overall safety summary[17,24]

	Encorafenib + cetuximab ($n = 216$)		Encorafenib + binimetinib + cetuximab ($n = 222$)		Control ($n = 193$)	
	Any grade	Grade ≥3	Any grade	Grade ≥3	Any grade	Grade ≥3
AE regardless of causality, *n* (%)						
Any AE	212 (98)	124 (57)	220 (99)	146 (66)	190 (98)	124 (64)
Any serious AE	86 (40)	74 (34)	110 (50)	97 (44)	77 (40)	67 (35)
Any AE leading to discontinuation of any one drug	26 (12)	24 (11)	36 (16)	25 (11)	33 (17)	24 (12)
Any AE leading to discontinuation of all drugs	20 (9)	19 (9)	21 (10)	17 (8)	21 (11)	
AEs leading to death on treatment, *n* (%)	8 (4)[a]	–	10 (5)[b]	–	8 (4)[c]	–
Median duration of exposure,[d] weeks	19	–	21	–	7	–

AE, adverse event.
[a] Included intestinal obstruction ($n = 2$), large intestine perforation ($n = 1$), gastrointestinal haemorrhage ($n = 1$), cardiorespiratory arrest ($n = 1$), sepsis ($n = 1$), and aspiration ($n = 2$); none of these events were considered related to treatment.
[b] Included duodenal perforation ($n = 1$), gastrointestinal perforation ($n = 1$), ileus ($n = 1$), intestinal obstruction ($n = 1$), large intestine perforation ($n = 1$), hepatic failure ($n = 3$), cardiac arrest ($n = 1$), and septic shock ($n = 1$); among these, one event was considered related to treatment (large intestine perforation).
[c] Included subileus ($n = 1$), cardiorespiratory arrest ($n = 1$), lung infection ($n = 1$), peritonitis ($n = 1$), *Pneumocystis jirovecii* pneumonia ($n = 1$), anaphylactic reaction ($n = 1$), cerebral ischemia ($n = 1$), and respiratory failure ($n = 1$); among these, two events were considered related to treatment (anaphylaxis, respiratory failure).
[d] Median duration of exposure calculated using Kaplan–Meier method.

Table 2. Summary of most common AEs with encorafenib plus cetuximab (≥10% of patients for any grade, ≥3% for grade ≥3 in the encorafenib + cetuximab group)[17]

	Encorafenib + cetuximab (n = 216)		Control (n = 193)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Any AE[a], *n* (%)	212 (98)	124 (57)	190 (98)	124 (64)
Gastrointestinal AEs, *n* (%)				
Diarrhoea	83 (38)	6 (3)	94 (49)	20 (10)
Nausea	82 (38)	1 (<1)	84 (44)	3 (2)
Decreased appetite	67 (31)	3 (1)	56 (29)	6 (3)
Abdominal pain	60 (28)	7 (3)	54 (28)	10 (5)
Vomiting	59 (27)	3 (1)	61 (32)	6 (3)
Constipation	39 (18)	0	39 (20)	2 (1)
Abdominal pain upper	22 (10)	2 (1)	15 (8)	1 (<1)
Intestinal obstruction	14 (6)	10 (5)	8 (4)	5 (3)
Skin and subcutaneous tissue AEs, *n* (%)				
Dermatitis acneiform	65 (30)	1 (<1)	77 (40)	5 (3)
Melanocytic nevus	34 (16)	0	0	0
Rash	32 (15)	0	28 (15)	3 (2)
Dry skin	28 (13)	0	16 (8)	1 (<1)
Pruritus	24 (11)	0	10 (5)	0
Musculoskeletal and connective tissue AEs, *n* (%)				
Arthralgia	49 (23)	3 (1)	3 (2)	0
Myalgia	33 (15)	1 (<1)	4 (2)	0
Musculoskeletal pain	29 (13)	0	5 (3)	0
Back pain	28 (13)	3 (1)	27 (14)	2 (1)
General/other AEs, *n* (%)				
Fatigue	72 (33)	9 (4)	54 (28)	9 (5)
Asthenia	52 (24)	8 (4)	53 (27)	10 (5)
Headache	43 (20)	0	5 (3)	0
Pyrexia	40 (19)	3 (1)	28 (15)	1 (<1)
Dyspnoea	28 (13)	2 (1)	20 (10)	6 (3)
Hypomagnesaemia	25 (12)	1 (<1)	19 (10)	3 (2)
Pain in extremity	25 (12)	0	2 (1)	0
Weight decreased	24 (11)	1 (<1)	12 (6)	0
Insomnia	24 (11)	0	13 (7)	0
Oedema peripheral	23 (11)	0	14 (7)	1 (<1)
Blood and lymphatic system disorders, *n* (%)				
Anaemia	42 (19)	12 (6)	36 (19)	13 (7)
Abnormal laboratory values[b], *n* (%)				
Creatinine (μmol/l), hyper	116 (54)	7 (3)	73 (38)	2 (1)
Haemoglobin (g/l), hypo	85 (39)	12 (6)	89 (46)	10 (5)
Bilirubin (μmol/l), hyper	18 (8)	6 (3)	17 (9)	6 (3)

Table adapted from Tabernero J, et al. *J Clin Oncol* 2021;39:273-84.
AE, adverse event.
[a] Regardless of causality; AEs of any grade that occurred in ≥10% of patients in the encorafenib + cetuximab arm; grade ≥3 AEs that occurred in ≥3% of patients in the encorafenib + cetuximab arm.
[b] Selected laboratory abnormalities associated with AEs.

(38%), nausea (38%), decreased appetite (31%), abdominal pain (28%), and vomiting (27%)]. Other commonly reported AEs of any grade with encorafenib plus cetuximab included fatigue (33%), dermatitis acneiform (30%), asthenia (24%), arthralgia (23%), and headache (20%). The most common grade ≥3 AEs with encorafenib plus cetuximab were anaemia (6%), intestinal obstruction (5%), fatigue (4%), asthenia (4%), diarrhoea (3%), and abdominal pain (3%). Common laboratory abnormalities included high creatinine (any grade: 54%, grade 3-4: 3%) and low haemoglobin (any grade: 39%, grade 3-4: 6%).

Management of AEs with encorafenib plus cetuximab in clinical practice

In this section, further details are given on the most commonly reported AEs with encorafenib plus cetuximab in the BEACON CRC study, together with recommendations for their management in clinical practice.

When initiating a new cancer treatment, patients and their caregivers should be made aware of potential AEs and how to proactively manage them when possible. For specific anticipated AEs, such as skin-related reactions, appropriate prophylaxis may be warranted to minimise the impact of such events.[25] Patients should be advised to quickly alert their cancer team and other health care professionals if they experience persistent side-effects or if any symptoms change or worsen. When certain AEs occur at specific severities or are persistent, modification or interruption of encorafenib or cetuximab doses may be considered.[13,14,19,20] Dosage modification guidance is shown in Table 3 for encorafenib and Supplementary Table S2, available at https://doi.org/10.1016/j.esmoop.2021.100328, for cetuximab.

Gastrointestinal AEs

Gastrointestinal disorders, including diarrhoea, nausea, and vomiting, were among the most commonly reported AEs for encorafenib plus cetuximab in patients with mCRC (Table 2), consistent with the typical, contrasting gastrointestinal side-effects associated with each drug.[14,19] Most events were grade 1-2 (mild or moderate) and occurred less frequently in the encorafenib plus cetuximab group than in the control group (Table 2). Gastrointestinal AEs were rarely associated with discontinuation or dosage reductions (Table 4). In the encorafenib plus cetuximab group, discontinuation of either study drug due to gastrointestinal AEs occurred in 4% of patients: due to diarrhoea, abdominal pain, and gastric haemorrhage in one patient each, due to intestinal perforation in two patients, and due to intestinal obstruction in three patients (Table 4). All were grade ≥3 except for one instance of gastric haemorrhage in one patient. Reduction of encorafenib dosage due to gastrointestinal AEs occurred in 3% of patients: due to diarrhoea, vomiting, ileus, and pancreatitis in one patient each, and due to nausea in two patients (Table 4). All were grade ≥3, except one instance of diarrhoea and one instance of nausea in one patient each. No patients in the encorafenib plus cetuximab group received a reduction in cetuximab dosage due to gastrointestinal AEs. In clinical practice, gastrointestinal AEs should be proactively managed with dietary modifications and increased fluid intake (Table 5).[26,27] Supportive medications, such as loperamide, may be beneficial for diarrhoea, and antiemetics may be considered for nausea and vomiting (Table 5).[26,27]

Skin AEs

Skin AEs were common with encorafenib plus cetuximab; most were mild or moderate (Table 2) and did not result in any discontinuations of either drug (Table 4). Due to its effect on the EGFR pathway, cetuximab is associated with dermatologic AEs.[19,20] Typical skin AEs associated with cetuximab treatment, such as acneiform rash,[19,20] were less frequent in patients in the encorafenib plus cetuximab

Table 3. Encorafenib modification and reduction guidance[13,14,a]

AE	Dose modification
Gastrointestinal, arthralgia/myalgia, renal, fatigue, asthenia, headache, and pyrexia	• For recurrent grade 2 or first occurrence of any grade 3 event, withhold encorafenib for up to 4 weeks ○ If event improves to grade 0-1 or to baseline level, then resume encorafenib at reduced dose ○ If no improvement, permanently discontinue encorafenib[b] • For first occurrence of any grade 4 event, permanently discontinue encorafenib[b] or withhold encorafenib for up to 4 weeks ○ If event improves to grade 0-1 or to baseline level, then resume encorafenib at reduced dose ○ If no improvement, permanently discontinue encorafenib[b]
Skin (other than hand-foot skin reaction)[c]	• For grade 2, if no improvement within 2 weeks, withhold encorafenib until grade 0-1, then resume at same dose • For grade 3, withhold encorafenib until grade 0-1, then resume at same dose if first occurrence or reduce dose if recurrent • For grade 4, permanently discontinue encorafenib[b]
Dose reduction steps	
• First dose reduction: 225 mg orally once daily • Second dose reduction: 150 mg orally once daily • Subsequent modification: permanently discontinue[b] if unable to tolerate 150 mg once daily	

AE, adverse event.
[a] For full details on dosage modifications, please consult the Prescribing Information or Summary of Product Characteristics.[13,14]
[b] If encorafenib is permanently discontinued, cetuximab should also be discontinued; if cetuximab is discontinued, encorafenib should also be discontinued.
[c] Dose modification is not recommended for new primary cutaneous malignancies.

group than patients in the control group who received cetuximab (any-grade dermatitis acneiform: 30% versus 40%; grade ≥3: <1% versus 3%; Table 2). Melanocytic nevi and pruritus, which are typically associated with encorafenib treatment,[14] were more common in patients in the encorafenib plus cetuximab group than in patients in the control group (any-grade melanocytic nevus: 16% versus 0%; any-grade pruritus: 11% versus 5%;). Other common skin AEs of any grade with encorafenib plus cetuximab included rash [15% (versus 15% with control)] and dry skin [13% (versus 8% with control); Table 2]. Dosage reductions due to any skin-related AEs were rare (Table 4); acneiform dermatitis of grade 1-2 led to encorafenib dosage reduction in 1% (2/216) of patients and rash pustular of grade 1 led to cetuximab dosage reduction in <1% (1/216) of patients. Cetuximab is also associated with an increased risk of secondary infection[19,20]; however, severe skin reactions were rare with encorafenib plus cetuximab combination therapy.

These events should be carefully monitored and addressed through both prophylaxis and active management to ensure patients can remain on treatment.[25,28] Prophylactic measures may be more effective than reactive measures for skin-related AEs.[25] For EGFR inhibitor-driven skin reactions, recommended prophylactic options include providing patients with guidance on general basic skin cleansing, use of sun protection, application of topical skin care, and use of oral antibiotics (Table 5).[25] In clinical

Table 4. Incidence of dose reductions and discontinuation rates for commonly reported AEs[a] in the BEACON CRC study[24]

	Encorafenib + cetuximab (n = 216)		Control (n = 193)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Gastrointestinal AEs				
Dose reduction due to any GI AE, %				
Encorafenib	3[b]	2	NA	NA
Cetuximab	0	0	2[c]	1
Discontinuation of any study drug due to any GI AE, %	4[d]	3	5[e]	3
Skin AEs[f]				
Dose reduction due to any skin AE, %[g]				
Encorafenib	1	0	NA	NA
Cetuximab	0	0	2	1
Discontinuation of any study drug due to any skin AE, %[g]	0	0	2	1
Arthralgia/myalgia AEs				
Dose reductions, %				
Encorafenib				
Arthralgia	1	<1	NA	NA
Myalgia	<1	0	NA	NA
Cetuximab	0	0	0	0
Discontinuation of any study drug due to arthralgia or myalgia, %	0	0	0	0
Renal AEs				
Dose reduction of any study drug due to any renal or urinary disorder, %	0	0	0	0
Discontinuation of any study drug due to any renal or urinary disorder, %[h]	1	1	0	0
Other AEs				
Dose reductions, %				
Encorafenib[i]				
Fatigue	1	0	NA	NA
Asthenia	1	<1	NA	NA
Cetuximab	0	0	0	0
Discontinuation of any study drug, %[j]				
Fatigue	<1[k]	<1[k]	<1[k]	0
Asthenia	0	0	1	0

AE, adverse event; GI, gastrointestinal; NA, not available.
[a] Regardless of causality; data indicate percentage of patients.
[b] Due to diarrhoea (n = 1), nausea (n = 2), vomiting (n = 1), ileus (n = 1), and pancreatitis (n = 1).
[c] Due to diarrhoea (n = 3) and stomatitis (n = 1).
[d] Due to diarrhoea (n = 1), abdominal pain (n = 1), intestinal obstruction (n = 2), small intestinal obstruction (n = 1), gastric haemorrhage (n = 1), intestinal perforation (n = 1), and large intestine perforation (n = 1).
[e] Due to diarrhoea (n = 2), intestinal obstruction (n = 1), small intestinal obstruction (n = 3), subileus (n = 1), vomiting (n = 1), abdominal hernia (n = 1), faeces soft (n = 1), flatulence (n = 1), and stomatitis (n = 2).
[f] Patients in the control arm did not receive routine skin evaluations per protocol.
[g] Due to any skin AEs.
[h] Two patients discontinued due to acute kidney injury (one cetuximab; one both study drugs).
[i] No dose reductions were necessary for pyrexia or headache.
[j] There were no discontinuations of any drug due to pyrexia or headache.
[k] One patient discontinued cetuximab as a result of fatigue.

practice, rash associated with encorafenib plus cetuximab may be managed with topical agents according to severity, or with oral agents if required (Table 5).[28] It may also be advisable to seek guidance from a dermatologist for persistent dermatologic AEs. Dosage modifications may be considered for encorafenib and/or cetuximab according to the severity, persistence, and recurrence of skin AEs (Table 3; Supplementary Table S2, available at https://doi.org/10.1016/j.esmoop.2021.100328).[13,14,19,20]

Table 5. Management of frequently reported AEs with encorafenib plus cetuximab

AE	Signs and symptoms	Supportive care, monitoring, and management
Diarrhoea[26,27,29]	Dehydration, electrolyte imbalance, low immune function, malnutrition, inflammation, abdominal pain	• Rule out alternative causes (e.g. infection) • Dietary modification (frequent, small meals) • Reduce fibre consumption • Increase fluid intake • Replacement of lost salts • Consider treatment with loperamide
Nausea/vomiting[26]	Dehydration, electrolyte imbalance, weakness, weight loss	• Avoid fried and spicy foods • Small, frequent meals • Lukewarm or cold foods • Remain sitting up or standing within 1 h after eating • Maintain oral hygiene • Prevent dehydration • Antiemetics [e.g. dexamethasone, 5-hydroxytryptamine (serotonin)-3 antagonist, lorazepam, metoclopramide]
Skin (excludes hand-foot reaction)[25,28]	Acneiform dermatitis: macular or papular rash; itching; desquamation or lesions; macular, papular, or vesicular eruption; generalised ulcerative, exfoliative, or bulbous dermatitis	• Consider prophylactic measures (e.g. advice on cleansing, use of sun protection, application of topical skin care, use of oral antibiotics) • Avoid sun exposure • Mild rash: use topical corticosteroids (e.g. mometasone cream) and/or topical antibiotic (e.g. erythromycin) • Moderate rash: use topical erythromycin or clindamycin plus topical mometasone or topical pimecrolimus plus oral antibiotics • Severe rash: consider oral prednisolone or oral isotretinoin
	Cutaneous malignancies	• Carry out dermatologic evaluations before initiating treatment, every 2 months during treatment and for up to 6 months following discontinuation of treatment[15,16] • Manage suspicious skin lesions with excision and dermatopathologic evaluation[15,16]
Myalgia/arthralgia[28,29,33]	Muscle pain, joint pain	• Rest area with pain • Recommend use of pain relievers • Consider stretching • Consider low-dose corticosteroids for severe symptoms
Renal AEs	Decreased urination, elevated creatinine	• Maintain adequate fluid intake during treatment • Consider avoiding all nephrotoxic medications • Ensure any concurrent urinary tract infections are promptly treated according to general treatment guidelines • Evaluate patients for other causes of renal dysfunction and treat accordingly • Seek nephrologist consultation as required
Other (fatigue, asthenia, headache, pyrexia)[29,31,32]		• Maintain adequate hydration and healthy diet • Exercise regularly if possible • Rest when needed • Recommend use of pain relievers to manage symptoms as appropriate • For pyrexia, rule out alternative causes (e.g. infection)

AE, adverse event.

Dermatologic malignancies. New primary melanoma (malignant melanoma or malignant melanoma *in situ*) occurred in 2% (4/216) of patients receiving encorafenib plus cetuximab in the BEACON CRC study. All cases were resolved (by procedure in three patients, and by concomitant medication and procedure in one patient). The incidence of keratoacanthoma was 1% (2/216), which is lower than that observed with BRAF inhibitor monotherapy.[29,30] To monitor for cutaneous malignancies, dermatologic evaluations are recommended before initiating treatment with encorafenib plus cetuximab, every 2 months during treatment, and for up to 6 months following discontinuation of treatment (Table 5).[13,14] Any suspicious skin lesions should be managed with excision and dermatopathologic evaluation.[13,14] The modification of encorafenib dosage is not recommended for new primary cutaneous malignancies.[13,14]

Myalgia and arthralgia

Arthralgia and myalgia, which are commonly associated with encorafenib and a class effect of BRAF inhibitors,[14] occurred in 23% and 15% of patients receiving encorafenib plus cetuximab, respectively (Table 2). Most of these events were grade 1-2; grade $\geq$3 arthralgia occurred in 1% of patients and grade $\geq$3 myalgia in $<$1% of patients. Myalgia and arthralgia each led to encorafenib dosage reductions in $\sim$1% of patients; they did not lead to cetuximab dosage reductions or discontinuation of either study drug (Table 4). In clinical practice, patients with arthralgia or myalgia should be advised to rest the area(s) with pain and consider use of anti-inflammatory pain relievers (Table 5).[28] For patients with severe symptoms, encorafenib dosage can be modified (Table 3).[13,14] Low-dose corticosteroids (e.g. prednisone 5 mg) may also be given to avoid encorafenib dosage reduction.[29]

Renal AEs

The most common renal AE of any grade was urinary tract infection, which occurred in 8% of patients receiving encorafenib plus cetuximab and in 3% of patients in the control group (grade ≥3: 2% and 1%, respectively). Elevated creatinine levels of any grade occurred in 54% of patients (grade 3-4: 3%) receiving encorafenib plus cetuximab, which was higher than in the control group (38% of patients; grade 3-4: 1%) (Table 2). Increased creatinine greater than the upper limit of normal occurred in 3% of patients in the encorafenib plus cetuximab group and in 1% of the control group. Two patients (1%) receiving encorafenib plus cetuximab discontinued treatment due to acute kidney injury (one patient discontinued cetuximab; one patient discontinued both study drugs); however, there were no dosage modifications due to renal or urinary disorders (Table 4).

Analyses of BRAF inhibitor clinical studies have indicated that effects on the renal system may be a class effect common to agents targeting this pathway.[22] As such, patients should be advised on adequate hydration and other key considerations before starting treatment with encorafenib plus cetuximab. In clinical practice, avoiding all nephrotoxic medications is commonly advised. Any concurrent urinary tract infections should be treated according to local guidelines. Patients should be evaluated for other causes of renal dysfunction. Gastrointestinal AEs such as diarrhoea, nausea, and vomiting should be promptly and effectively managed to prevent dehydration. Treatment with encorafenib and cetuximab should be halted for moderate-to-severe renal dysfunction, and nephrology consult should be considered (Table 5).

Other AEs including fatigue, asthenia, headache, and pyrexia

Fatigue/asthenia. In the encorafenib plus cetuximab group, fatigue of any grade occurred in 33% of patients (grade ≥3: 4%) and asthenia of any grade occurred in 24% of patients (grade ≥3: 4%) (Table 2). One patient (<1%) discontinued cetuximab as a result of grade 3 fatigue (Table 4). With regard to dosage modifications, fatigue led to the reduction of encorafenib dosage in 1% of patients (2/216; both due to grade 2 fatigue) and asthenia led to reduction of encorafenib dosage in 1% of patients (3/216; 2 due to grade 2 asthenia, 1 due to grade 3 asthenia) (Table 4). In clinical practice, fatigue and asthenia can be managed with standard supportive care (Table 5).[31,32]

Headache. Headache occurred in 20% of patients receiving encorafenib plus cetuximab; all were grade 1-2 (Table 2) and there were no discontinuations or dosage modifications of either drug due to headache. In clinical practice, headache can be managed with standard supportive care (Table 5).[31,32]

Pyrexia. Pyrexia of any grade occurred in 19% of patients receiving encorafenib plus cetuximab; grade ≥3 pyrexia occurred in 1% of patients (Table 2). There were no discontinuations or dosage modifications of either study drug due to pyrexia. In clinical practice, pyrexia can be managed with standard supportive care (Table 5).[31,32]

DISCUSSION

In the BEACON CRC study, encorafenib plus cetuximab improved overall survival and objective response rates relative to control therapy in patients with previously treated *BRAF* V600E mCRC.[16,17] This combination is recommended in the National Comprehensive Cancer Network guidelines.[15] AEs that occurred with encorafenib plus cetuximab during the study were generally mild or moderate in severity and manageable with supportive care.[16,17] Most AEs were grade 1 or 2 in severity and rarely required study drug discontinuation, suggesting that these events may resolve over time. In addition, dosage adjustments were infrequent, and most patients were able to continue at the preferred dosage of both agents. Commonly reported AEs with encorafenib plus cetuximab in the BEACON CRC study included gastrointestinal AEs, skin AEs, arthralgia, myalgia, renal events, fatigue, asthenia, headache, and pyrexia. Cutaneous malignancies were rare, and all cases resolved. This profile of AEs is expected based on the individually known profiles of cetuximab and encorafenib and their mechanisms of action.[13,14,19,20] This knowledge can help to anticipate these events in clinical practice and provide patients with effective, practical supportive care options. In clinical practice, AE management strategies can be employed to help mitigate the impact of these AEs related to encorafenib and cetuximab.

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DISCLOSURE

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ETHICS APPROVAL

The BEACON CRC study was conducted in accordance with the requirements of each country's regulatory authorities as well as the provisions of the Declaration of Helsinki and Good Clinical Practice guidelines, as defined by the International Council for Harmonisation. All patients who participated in the trial provided written informed consent. This trial was approved by the institutional review board or independent ethics committee at each centre.

DATA SHARING

The majority of data presented are from previously published sources. A small amount of unpublished data from the BEACON CRC study has been included and is not publicly available.

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