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Review

Nursing care and management of adverse events for patients with $BRAF^{V600E}$-mutant metastatic colorectal cancer receiving encorafenib in combination with cetuximab: a review

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Received: 8 July 2022 / Accepted: 5 January 2023

Abstract

Encorafenib is a B-Raf proto-oncogene serine/threonine-protein kinase (BRAF) inhibitor, approved in the EU and USA, in combination with the epidermal growth factor receptor (EGFR) inhibitor cetuximab, for the treatment of patients with $BRAF^{V600E}$-mutant metastatic colorectal cancer (mCRC). In the pivotal BEACON CRC trial, patients achieved longer survival with encorafenib in combination with cetuximab vs. conventional chemotherapy. This targeted therapy regimen is also generally better tolerated than cytotoxic treatments. However, patients may present with adverse events unique to the regimen and characteristic of BRAF and EGFR inhibitors, which produce their own set of challenges. Nurses play an essential role in navigating the care of patients with $BRAF^{V600E}$-mutant mCRC and managing adverse events that patients may experience. This includes early and efficient identification of treatment-related adverse events, subsequent management of adverse events and education of patients and their caregivers around key adverse events. This manuscript aims to provide support to nurses managing patients with $BRAF^{V600E}$-mutant mCRC receiving encorafenib in combination with cetuximab, by summarising potential adverse events and providing guidance on how to manage them. Special attention will be paid to the presentation of key adverse events, dose modifications that may be required, practical recommendations and supportive care measures.

Keywords

Nursing role
BRAF Mutation
Encorafenib
Cetuximab
Toxicity
Colorectal cancer

Abbreviations

ADL Activities of daily living
ALP Alkaline phosphatase
ALT Alanine aminotransferase increase
AST Aspartate aminotransferase increase
BL Baseline
BRAF B-Raf proto-oncogene serine/threonine-protein kinase
BRAF (gene) v-Raf murine sarcoma viral oncogene homolog B
$BRAF^{WT}$ BRAF wild type
BRAT Bananas, rice, apples and toast
BSA Body surface area
CK Creatine kinase
CRC Colorectal cancer
CT Computed tomography
ECG Electrocardiogram
EGFR Epidermal growth factor receptor
FOLFIRI Folinic acid, fluorouracil and irinotecan
Hb Haemoglobin
IV Intravenous
LLN Lower limit of normal
MAPK Mitogen-activated protein kinase
mCRC Metastatic colorectal cancer
NA Not applicable
OS Overall survival

QTc Corrected QT interval
RAS Rat sarcoma virus
ULN Upper limit of normal

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1007/s00520-023-07579-9.

Background

In AQ1 Europe, colorectal cancer (CRC) is both the second most diagnosed cancer and the second biggest cause of death, accounting for 500,000 cases and 138,000 deaths in 2018 [1]. Despite improved efforts in screening, it is estimated that > 20% of patients present with metastatic CRC (mCRC) and out of those diagnosed with localised CRC, 50–60% will go on to develop metastases [2, 3, 4]. This is a major contributor to the high death rates reported in CRC; the 5-year survival rate for mCRC is just 12% with a median overall survival (OS) of 30 months [4, 5, 6]. It is widely accepted that sporadic CRC arises due to accumulation of both genetic and epigenetic alterations of the genome. Particularly, CRC is associated with the activation of oncogenes, such as Kirsten rat sarcoma viral oncogene homolog and v-Raf murine sarcoma viral oncogene homolog B (BRAF), which have roles in regulating proliferation, differentiation and cell growth [7, 8]. These mutations not only help drive the development of CRC but can also act as biomarkers, determining prognosis and response to treatment [5]. Due to their predictive and prognostic roles, European guidelines recommend *RAS* and *BRAF* mutational testing upon diagnosis of mCRC [9].

BRAF mutations are present in 8–12% of mCRC cases; the majority of these (~ 95%) result from a valine to glutamate mutation known as V600E [5, 10]. The $BRAF^{V600E}$ mutation forms a protein that is 500-fold more active than wild-type BRAF ($BRAF^{WT}$) [11]. This results in constitutive activation of the mitogen-activated protein kinase (MAPK) signalling pathway through downstream phosphorylation of protein kinases, which drive tumour cell proliferation and survival [8]. $BRAF^{V600E}$-mutant mCRC is associated with right-sided primary tumours, advanced age, female sex, late-stage and aggressive disease that has a limited response to the standard of care treatment. In mCRC, $BRAF^{V600E}$ mutations are a key prognostic biomarker for poor outcomes resulting in a two-fold increase in mortality compared with $BRAF^{WT}$ mCRC [12].

Treating $BRAF^{V600E}$-mutant mCRC

Doub AQ2 let or triplet chemotherapy regimens plus the VEGF inhibitor, bevacizumab, are recommended as first-line treatment for $BRAF^{V600E}$-mutant mCRC. These cytotoxic combinations provide moderate benefits in first-line for $BRAF^{V600E}$-mutant mCRC, but limited benefits at second-line and beyond [8]. Therefore, European guidelines recommend a BRAF inhibitor, encorafenib, in combination with an epidermal growth factor receptor (EGFR) inhibitor, cetuximab, in patients with $BRAF^{V600E}$-mutant mCRC who have received prior systemic therapy [9]. Unlike in melanoma, responses to BRAF inhibitor monotherapy were suboptimal in $BRAF^{V600E}$-mutant mCRC. BRAF inhibition triggers a feedback loop in CRC cells, whereby rapid activation of upstream EGFR reinstates MAPK activation, resulting in continued cell proliferation [8, 13]. In preclinical and early clinical trials, addition of an EGFR inhibitor alongside a BRAF inhibitor resulted in synergistic inhibition of tumour growth, overcoming the feedback loop. Adding a MEK inhibitor has also reported a similar increase in anti-tumour activity [12, 14, 15, 16, 17].

These early trials prompted the pivotal Phase III, open-label BEACON CRC trial. Patients with $BRAF^{V600E}$-mutant mCRC who had received prior systemic therapy were randomly assigned 1:1:1 to receive encorafenib plus the MEK inhibitor, binimetinib, in combination with cetuximab (triplet), encorafenib in combination with cetuximab (doublet) or the investigators choice of irinotecan/fluorouracil, irinotecan and leucovorin plus cetuximab (control). Median OS was 9.3 months with both triplet and doublet combinations vs. 5.9 months for the control [8]. Overall response rate was greatest in the triplet group (26.8%) vs. the doublet (19.5%) and the control (1.8%). However, adverse events were also highest in the triplet group compared with doublet and control regimens, with grade ≥ 3 adverse events reported in 65.8%, 57.4% and 64.2% of patients, respectively

[8]. It was concluded that the doublet regimen was sufficient to maximise OS benefit with an acceptable adverse event profile [8]. Data from BEACON CRC formed the basis for the EU and US approval of encorafenib in combination with cetuximab for patients with $BRAF^{V600E}$-mutant mCRC who had received prior systemic treatment [18, 19].

For mCRC, the recommended dose of encorafenib is 300 mg, taken orally as four 75 mg capsules once daily. Encorafenib does not need to be refrigerated and can be taken at home [20, 21]. Nurses may use telemonitoring to check patients are taking the medication as directed to ensure full benefit of encorafenib; telemonitoring has been applied to other patient groups, with significantly improved self-management and medication adherence [22, 23, 24].

The official administration guidelines recommend cetuximab is given as a weekly intravenous (IV) infusion, initially at 400 mg/m^2 (120-min infusion), then 250 mg/m^2 (60-min infusion) for subsequent doses. Weekly infusions mean frequent visits to the hospital for patients, perpetuating treatment fatigue. Consequently, some centres administer cetuximab bi-weekly, which is more convenient for both the patient and treating institution [25, 26, 27]. Available data suggest bi-weekly cetuximab, at 500 mg/m^2, has an equivalent pharmacokinetic, efficacy and safety profile to weekly administration. However, these results come from patients treated with cetuximab alongside chemotherapy and not encorafenib, so further data are needed to confirm the efficacy of bi-weekly cetuximab in this setting [25, 26, 27].

In general, targeted treatments are better tolerated than conventional cytotoxic agents. However, their characteristic patterns of adverse events differ from conventional treatment, presenting unique challenges [28]. Nurses are crucial in educating patients and caregivers on the disease, available treatments and the nature, recognition and severity of any possible adverse events. This can help ensure potential adverse events are managed promptly so maximum treatment benefit is achieved. The objective of this manuscript is to provide an overview of adverse events observed in patients with $BRAF^{V600E}$-mutant mCRC receiving encorafenib in combination with cetuximab, guidance on adverse event management, suggestions for supportive care to aid the management and prevention of adverse events, and tips for educating patients and caregivers.

Encorafenib in combination with cetuximab: overview of adverse events

The most frequently occurring adverse events reported with BRAF inhibitors are dermatological and can develop within days of treatment [8, 29, 30]. Pyrexia can also occur following BRAF inhibitor treatment and may be due to an inflammatory response [8, 29, 30, 31]. Similarly, arthralgia, commonly reported in patients receiving BRAF inhibitors, may originate from this inflammatory response [8, 29, 30, 32]. Gastrointestinal events are also commonly associated with BRAF inhibitors. The MAPK pathway has a role in regulating chloride secretion in normal gastrointestinal mucosa and therefore BRAF inhibition may increase chloride secretion, inducing diarrhoea [8, 33]. Cardiovascular side effects have been associated with BRAF inhibitors, possibly due to non-specific interference with MAPK signalling. In cardiovascular cells, MAPK inhibition leads to oxidative stress and cell death, affecting the formation of blood vessels [30, 33, 34].

As with BRAF inhibitors, the most frequently occurring adverse events associated with EGFR inhibitors are skin disorders, although they present differently. This association with skin disorders is not surprising as EGFR is involved in the development and physiology of the epidermis. Evidence suggests an association between EGFR inhibitors and mucosal toxicity, possibly due to immunological factors [28]. Electrolyte imbalances, particularly hypomagnesaemia, often arise from compromised renal magnesium retention and are frequently reported in patients receiving cetuximab. The IV administration of cetuximab may also be associated with potentially severe infusion-related reactions; for example, anaphylactic reactions are assumed to be because of non-specific cytokine release from immune cells [28].

Table 1 summarises the most frequent adverse events seen in patients with $BRAF^{V600E}$-mutant mCRC receiving encorafenib in combination with cetuximab in BEACON CRC. Diarrhoea was the most frequently reported adverse event of any grade, followed by nausea and fatigue. Among abnormal laboratory values associated with adverse events, creatinine increase (54%) and haemoglobin decrease (39%) were very

common [8]. The National Cancer Institute Common Terminology Criteria for Adverse Events and associated grading scales for key adverse events observed in this setting can be found in the supplementary material.

Table 1

The most AQ3 common adverse events observed with encorafenib in combination with cetuximab in the BEACON CRC trial [8]

Adverse events occurring in ≥ 20% (any grade) or ≥ 3% (grade ≥ 3)[a]%	Encorafenib in combination with cetuximab *n* = 216		Control[b] *n* = 193	
	Any grade	Grade ≥ 3	Any grade	Grade ≥ 3
Diarrhoea	38	3	49	10
Nausea	38	< 1	44	2
Fatigue	33	4	28	5
Decreased appetite	31	1	29	3
Dermatitis acneiform	30	< 1	40	3
Abdominal pain	28	3	28	5
Vomiting	27	1	32	3
Asthenia	24	4	28	5
Arthralgia	23	1	2	0
Headache	20	0	3	0
Selected abnormal laboratory values associated with adverse events, %				
Creatinine increase	54	3	38	1
Haemoglobin decrease	39	6	46	5
Bilirubin increase	8	3	9	3

[a]Regardless of causality; any-grade adverse events that occurred in ≥ 20% of patients receiving encorafenib in combination with cetuximab; grade ≥ 3 adverse events that occurred in ≥ 3% of patients receiving encorafenib in combination with cetuximab

[b]Patients in the control group received either investigator's choice of cetuximab and irinotecan or cetuximab and FOLFIRI (folinic acid, fluorouracil and irinotecan). *CRC* colorectal cancer

Encorafenib in combination with cetuximab: guidance for managing adverse events

General guidance should be given to patients commencing treatment with encorafenib in combination with cetuximab to minimise adverse events and maximise treatment efficacy. During treatment with encorafenib, patients are advised to keep hydrated. Encorafenib should be taken ~~the same hour every~~at the same time every day, and the capsule swallowed whole with water. If a dose is missed, it can be taken up to 12 h before the next dose. If taken within 12 h of the next dose, patients should skip that dose and take their next dose at the regular time [20].

Certain medicinal products, such as ritonavir, itraconazole, clarithromycin, telithromycin, posaconazole and hormonal contraceptives, should be co-administered with caution and grapefruit juice should be avoided due to interaction with the enzyme CYP3A4, which metabolises encorafenib, or the enzyme UGT1A1, which is inhibited by encorafenib. The full list of medicinal products to be administered with caution can be found in the BRAFTOVI® SmPC [20].

Encorafenib may reduce the efficacy of hormonal contraceptives; therefore, alternative methods, such as barrier contraception, should be used during encorafenib treatment and for ≥ 1 month after the last dose. Females should not receive treatment if pregnant or breastfeeding. Males should be informed of the potential risk for impaired sperm production [20].

Prior to the first infusion of cetuximab, healthcare professionals must ensure the patient takes premedication consisting of an antihistamine and a corticosteroid at least 1 h before cetuximab administration. Premedication is recommended before all subsequent infusions. The patient must have the first cetuximab dose administered slowly (not exceeding 5 mg/min) and vital signs closely monitored for 2 h. Following doses can be infused

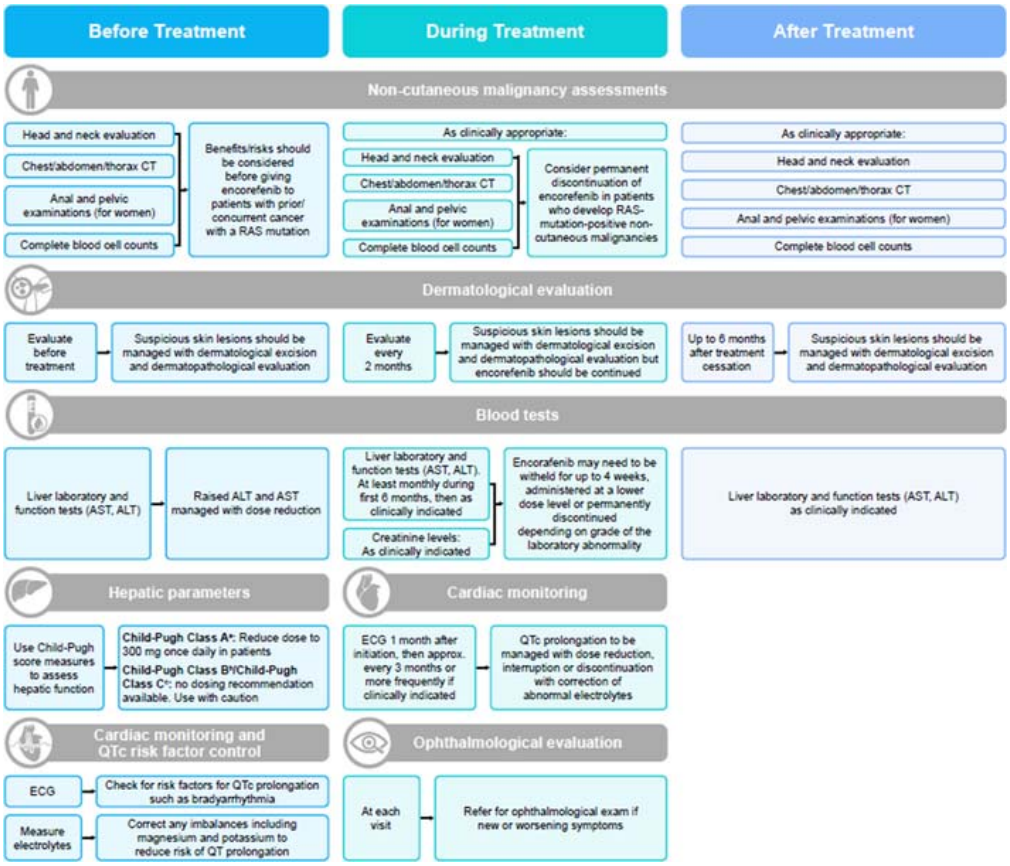
faster, without exceeding 10 mg/min, with close monitoring during and for at least 1 h afterwards. Resuscitation equipment should be available during this time [35]. It is crucial that patients are told to inform nurses immediately of any suspected side effects they may be experiencing at the time of infusion or during monitoring.

Infusion-related reactions may occur during the first infusion, up to several hours afterwards or during subsequent infusions. Patients should be monitored for signs of severe infusion-related reactions and should be warned of the potential for late-onset reactions. Symptoms can include bronchospasm, changes in blood pressure, itchy rash, loss of consciousness or shock and, in rare cases, chest pain leading to myocardial infarction or cardiac arrest. Patients should have their urea, serum electrolyte levels (including magnesium, potassium and calcium) and creatinine levels measured prior to each cetuximab treatment [35].

In clinical practice, several investigations are required before, during and after treatment with encorafenib in combination with cetuximab (Fig. 1). Dose and treatment schedules may need to be adapted according to the test outcomes to ensure the safety and efficacy of the regimen is maintained [20, 35].

Fig. 1

Recommendations for the monitoring of patients AQ4 along with appropriate actions before, during and after treatment with encorafenib in combination with cetuximab [20]. **a** Mild hepatic, **b** moderate hepatic impairment, **c** severe hepatic impairment. *ALT* alanine aminotransferase increase, *AST* aspartate aminotransferase increase, *CT* computed tomography, *ECG* electrocardiogram, *QTc* corrected QT interval, *RAS* rat sarcoma virus



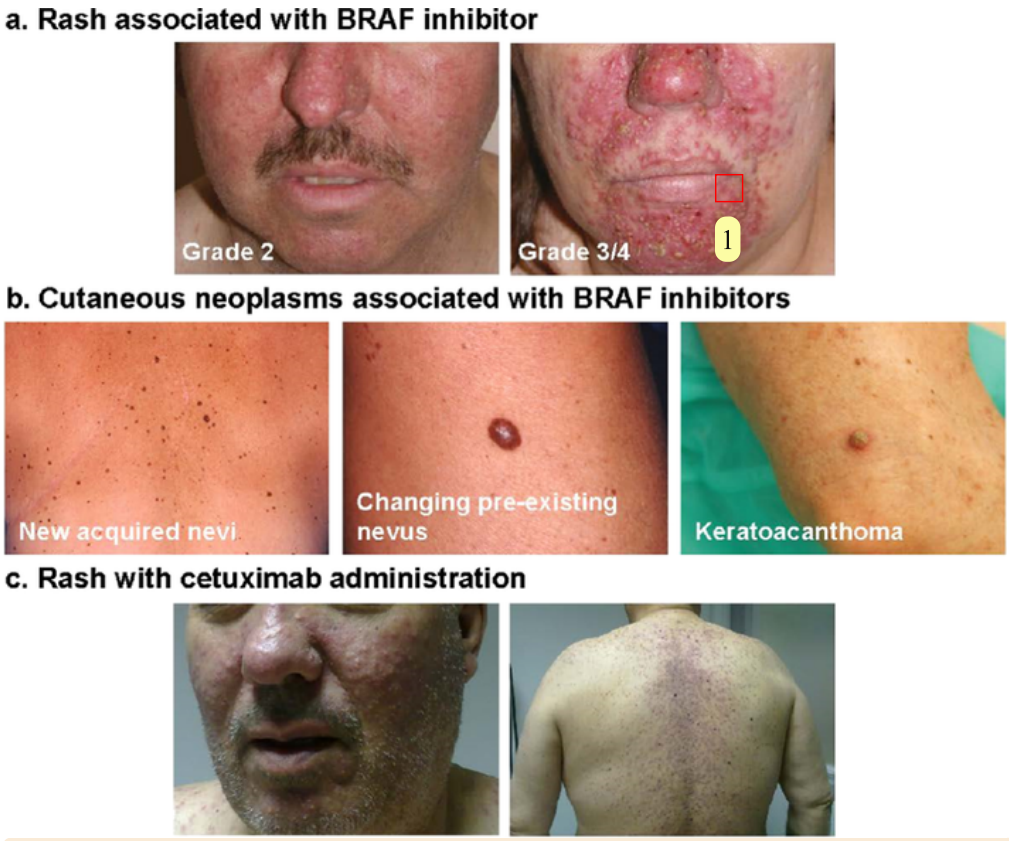
Skin conditions

Following treatment with encorafenib in combination with cetuximab, patients may experience skin reactions (Fig. 2). Skin rash, one of the most frequently occurring adverse events associated with BRAF inhibition, generally comprises several conditions, such as maculopapular exanthema, papulopustular exanthema and eczema [20, 33]. Melanocytic nevi are mostly benign neoplasms formed from the proliferation of pigment-producing cells in the skin [36]. During BRAF inhibition, pre-existing melanocytic nevi may change and new, eruptive nevi may also develop [37]. Changes in pre-existing melanocytic lesions usually do not have the $BRAF^{V600E}$ mutation but *BRAF* mutations are shown in up to 80% of acquired nevi [37, 38, 39, 40].

Melanocytic nevi associated with BRAF inhibitors have increased melanin pigmentation and deep HMB-45 expression (Fig. 2b) [37].

Fig. 2

Example images of skin disorders patients may experience when receiving encorafenib in combination with cetuximab [37, 41]. *BRAF* v-Raf murine sarcoma viral oncogene homolog B



1.Is this not a Cetuximab rash?

Acneiform dermatitis, a skin rash with a flat discoloured area or raised bumps resembling acne, frequently occurs in patients treated with cetuximab [20, 33, 35, 42]. Skin reactions develop in > 80% of patients who receive cetuximab, with ~ 15% classed as severe, including cases of skin necrosis [35].

Skin adverse events affected over three-quarters of patients receiving encorafenib in combination with cetuximab in BEACON CRC, which were predominantly mild or moderate (Table 2) [8]. Of the 216 patients receiving this treatment, 30% reported dermatitis acneiform of any grade, with one grade ≥ 3 event. Dose modifications and treatment discontinuations due to skin-related adverse events were rare in BEACON CRC [8].

Table 2

Dose reductions and discontinuations of encorafenib in combination with cetuximab due to key adverse events observed in the BEACON CRC trial [8, 43]

	Encorafenib in combination with cetuximab *n* = 216		Control[a,b] *n* = 193	
	Any grade	Grade ≥ 3	Any grade	Grade ≥ 3

	Encorafenib in combination with cetuximab $n = 216$		Control[a,b] $n = 193$	
	Any grade	Grade ≥ 3	Any grade	Grade ≥ 3
Skin-related adverse events				
Adverse event, %[c,d]				
Dermatitis acneiform	30	< 1	40	3
Melanocytic nevus	16	0	0	0
Rash	15	0	15	2
Dry skin	13	0	8	< 1
Pruritus	11	0	5	0
Dose reduction, %[c]				
Encorafenib	1	0	NA	NA
Cetuximab	0	0	2	1
Discontinuation of any study drug due to any skin adverse event, %[c]	0	0	2	1
Musculoskeletal-related adverse events				
Adverse event, %[c]				
Arthralgia	23	1	2	0
Myalgia	15	< 1	2	0
Musculoskeletal pain	13	0	2.6	0
Dose reduction, %[c]				
Encorafenib				
Arthralgia	1	< 1	NA	NA
Myalgia	< 1	0	NA	NA
Cetuximab	0	0	0	0
Discontinuation of any study drug due to any arthralgia or myalgia, %	0	0	0	0
Laboratory abnormalities				
Adverse event, %[c]				
ALT increase (IU/L)	19	< 1	30	4
AST increase (IU/L)	19	2	22	3
Bilirubin increase (mmol/L)	8	3	9	3
Creatine kinase increase (IU/L)	4	0	7	< 1
Creatinine increase (mmol/L)	54	3	38	1
Haemoglobin decrease (g/L)	40	6	46	5
General adverse events				
Adverse event, %[c]				
Fatigue	33	4	28	5
Asthenia	24	4	28	5
Headache	20	0	3	0
Pyrexia	19	1	15	< 1
Dyspnoea	13	1	10	3
Dose reduction, %[c]				
Encorafenib[e]				
Fatigue	1	0	NA	NA
Asthenia	1	< 1	NA	NA
Cetuximab	0	0	0	0
Discontinuation of any study drug, %				

	Encorafenib in combination with cetuximab $n = 216$		Control[a,b] $n = 193$	
	Any grade	Grade ≥ 3	Any grade	Grade ≥ 3
Fatigue	< 1[f]	< 1[f]	< 1[g]	0
Asthenia	0	0	1	0

ALT alanine aminotransferase increase, *AST* aspartate aminotransferase increase, *CRC*, colorectal cancer, *NA* not applicable

[a]Patients in the control group received either investigator's choice of cetuximab and irinotecan or cetuximab and folinic acid, fluorouracil and irinotecan (FOLFIRI)

[b]As per the protocol, patients in the control arm did not receive routine skin evaluations

[c]Regardless of causality; data indicate the percentage of patients

[d]Skin adverse events that occurred in ≥ 10% of patients receiving encorafenib in combination with cetuximab

[e]No dose reductions were required for pyrexia or headache

[f]One patient discontinued cetuximab as a result of fatigue; there were no discontinuations of any drug due to pyrexia or headache

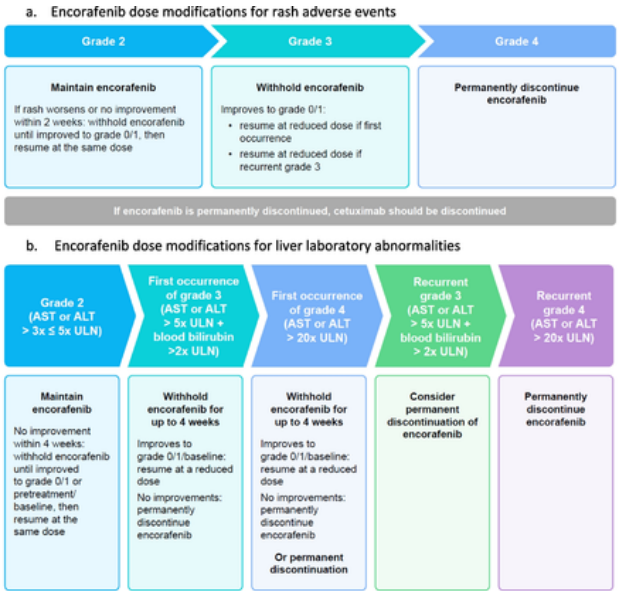
[g]There were no discontinuations of any drug due to pyrexia or headache

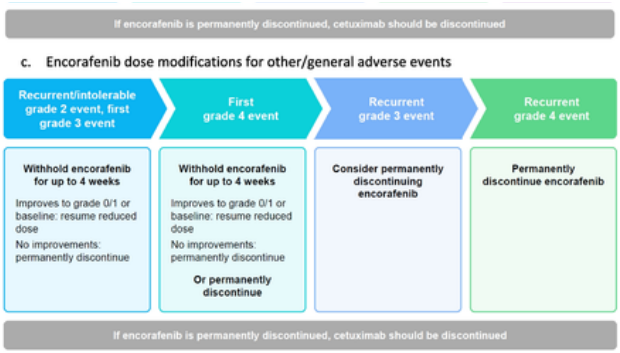
Monitoring and dose modifications

The severity of cutaneous adverse events may be overestimated by oncologists This is quite an inflammatory comment and should be reworded , causing premature discontinuation and reducing patient access to potentially lifesaving I would avoid use of this word as 'lifesaving' is rather false treatment [44, 45]. Therefore, an interdisciplinary approach between dermatologists, oncologists and oncology nurses trusted by the patient is imperative [45]. Dermatological evaluations should be performed prior to treatment with encorafenib in combination with cetuximab and every 4 weeks before a new encorafenib prescription is dispensed [20]. Patients may have their skin assessed more frequently and should be instructed to immediately inform their physicians or nurses if new skin lesions develop. Suspicious skin lesions should be managed with excision and dermatopathological evaluation [20, 35]. Encorafenib dose modification guidance for managing rash adverse events is shown in Fig. 3a. Modifications are not recommended for new primary cutaneous malignancies or melanocytic nevi [43].

Fig. 3

Encorafenib dose modifications for the management of key adverse events [20, 43]. **a** Encorafenib dose modifications for rash adverse events. **b** Encorafenib dose modifications for liver laboratory abnormalities. **c** Encorafenib dose modifications for other/general adverse events**.** ALT alanine aminotransferase increase, AST aspartate aminotransferase increase, *ULN* upper limit of normal





Cetuximab dose modification guidance is the same for any single type of skin adverse event. For grade ≥ 3, interrupt treatment until improvement to grade ≤ 2. At first incidence of severe skin reactions, treatment may resume at full dose when the reaction has resolved to grade ≤ 2. Following second and third occurrences of severe skin reactions, cetuximab must be interrupted and resumed at a lower dose level (200 mg/m^2 after second occurrence and 150 mg/m^2 after third) when resolved to grade ≤ 2. If severe skin reactions occur a fourth time or are not resolved to grade ≤ 2, permanent discontinuation is required [35].

Practical recommendations and supportive care measures

Many practical measures can be suggested to the patient to reduce the incidence and severity of skin adverse events [20, 43]. Some patients may require referral to dermatologists for skin biopsies but for optimal management of skin adverse events, dermatologist liaison is key [20, 43, 45]. Patients should avoid sun exposure, ensuring they wear a hat and sunscreen that blocks both ultraviolet A and ultraviolet B rays with SPF ≥ 30 [46]. Moisturising creams should be used at least twice daily, within 15 min of showering and with every hand wash. Creams containing salicylic acid, urea, ammonium or lactic acid are recommended as they soften skin and enable water retention [46, 47]. These creams may be administered prophylactically to prevent rashes or as treatment once the rash has developed. Products that can irritate or are abrasive to the skin, such as soaps, detergents, fragranced creams, sponges, bath scrubs and loofahs must be avoided [46].

For a mild rash, topical corticosteroids (e.g. mometasone cream) and/or topical antibiotics (e.g. erythromycin) may be required. If a moderate rash develops, topical erythromycin or clindamycin plus topical mometasone or topical pimecrolimus and oral antibiotics should be considered. For a severe rash, having consulted a dermatologist, oral prednisolone or oral isotretinoin may be used [43]. In addition, primary prophylaxis with doxycycline or minocycline may reduce the severity of rashes related to cetuximab [48].

For many patients, skin reactions negatively affect their body image and quality of life [42]. Forty-one percent of patients with CRC treated with cetuximab who developed a cutaneous skin rash reported psychological distress and in 47% of these cases, this affected their willingness to go out in public [49, 50]. Furthermore, patients reported facing a loss of privacy due to the rash increasing the difficulty of concealing an illness [45]. Therefore, it is imperative that emotional support and guidance are administered alongside physical treatment.

Musculoskeletal pain

Musculoskeletal side effects are common with encorafenib treatment, primarily arthralgia and myalgia. However, back pain, pain in extremities, muscular weakness and muscle spasms have also been reported [20, 32, 33]. In BEACON CRC, patients treated with encorafenib in combination with cetuximab experienced musculoskeletal pain (13%) arthralgia (23%) and myalgia (15%) [8]. Myalgia and arthralgia were generally mild or moderate in severity and grade ≥ 3 events were rare, resulting in very few dose modifications and no discontinuation of treatment (Table 2) [8, 43].

Monitoring and dose modifications

Encorafenib dose modification guidance for managing musculoskeletal events follows general adverse event

management guidance (Fig. 3b).

Practical recommendations and supportive care measures

For mild symptoms of arthralgia or myalgia, patients should be advised to rest the area of pain and consider stretching, gentle exercise, massage and relaxation techniques [51]. Pain relief or low-dose corticosteroids may be used. For severe musculoskeletal events, rheumatologists should be consulted as patients may require intra-articular or high-dose steroids [33].

Laboratory abnormalities

A range of laboratory abnormalities may be observed with encorafenib in combination with cetuximab [20]. The grading criteria for laboratory abnormalities are provided in the supplementary material.

Increases in liver laboratory values, alkaline phosphatase, bilirubin, alanine aminotransferase and aspartate aminotransferase may be observed with BRAF inhibitors [30]. In addition, creatinine elevation, which signifies impaired renal function, has been frequently reported with encorafenib monotherapy or in combination. Observed renal failure (acute kidney injury and renal impairment) is generally associated with vomiting and dehydration, due to contributing factors such as diabetes and hypertension. Elevated blood creatine kinase levels and decreased haemoglobin levels have similarly been reported in patients receiving encorafenib combinations [20].

Progressively decreasing serum magnesium levels and eventual hypomagnesaemia, due to lack of magnesium reabsorption in the kidneys, occurs frequently with cetuximab, potentially leading to heart arrhythmias, muscle weakness and psychotic symptoms [35, 52].

Over half of the patients in BEACON CRC experienced abnormal creatinine laboratory values when treated with encorafenib in combination with cetuximab. Renal, urinary and laboratory abnormalities in this group were largely mild and moderate in severity [8]. No events resulted in dose modification or discontinuation as renal or urinary adverse events were rare [43]. Liver and haematological laboratory abnormalities were more common in the control group compared with the encorafenib in combination with cetuximab group (Table 2) [8].

Monitoring and dose modifications

Reference ranges for laboratory values may vary between institutions. Therefore, nurses should be aware of their own centre's reference ranges. For renal abnormalities (Fig. 3b), blood creatinine should be monitored as clinically indicated and creatinine elevation managed with dose modification or discontinuation. For liver laboratory abnormalities (Fig. 3c), values should be monitored before initiation of encorafenib and at least monthly during the first 6 months, then as clinically indicated [8].

For the hypomagnesemia reported with cetuximab administration, electrolyte tests should be carried out prior to treatment, particularly for elderly patients, with re-examination once every 2–4 weeks [52]. If the patient presents with low magnesium, monitoring should increase to once weekly [53]. Grade 1 hypomagnesemia (< lower limit of normal − 1.2 mg/dL; < lower limit of normal − 0.5 mmol/L) is usually asymptomatic and does not require dose reduction. Magnesium replacement is required for grade ≥ 2 hypomagnesemia (< 1.2–0.9 mg/dL; < 0.5–0.4 mmol/L) [52, 54].

T his should be revisited with standardised perameters as it doesn't make sense

This is misleading; can we insert the range?

Practical recommendations and supportive care measures

Nurses should advise patients to maintain appropriate fluid intake during treatment. Any urinary tract infections should be treated promptly. Patients must be evaluated for alternative causes of renal dysfunction and treated accordingly. Nephrologist consultation should be ~~included~~considered as required [43].

For hypomagnesemia, oral magnesium replacement should be considered first as a sudden rise in serum magnesium concentrations (seen following IV infusions) reduces magnesium retention [55]. Oral magnesium salts often cause or worsen diarrhoea and nurses should advise administration with or after food to minimise incidence and severity. If oral magnesium is not appropriate, a parenteral magnesium replacement can be considered using a magnesium sulphat IV Magnesium replacement is often the mainstay of treatment here so I think we need to tread cautiously stating oral is predominantly the preferred option as patients can die from low Magnesiums e ~~injection~~infusion [55]. Follow-up blood tests should be taken as indicated by the patient's medical team.

General adverse events

General disorders, such as fatigue, dyspnoea, pyrexia and headaches, are frequently reported with single-agent BRAF inhibitors or in combination [20, 30]. Fatigue is associated with many oral kinase inhibitors [30]. The effects are often downplayed, but chronic fatigue can have a damaging impact on quality of life and may increase as treatment progresses [30, 56]. Nurses should consider other contributing factors, including disease progression, infection, depression, haematological and biochemical laboratory abnormalities, and increased hospital visits, all of which are physically and mentally draining [30, 56].

Around a third of patients in BEACON CRC experienced fatigue when treated with encorafenib in combination with cetuximab, 20% experienced headaches and 19% experienced pyrexia. These events rarely required dose modifications or discontinuations (Table 2) [8, 43].

Monitoring and dose modifications

Encorafenib dose modifications for managing general adverse events are shown in Fig. 3b. Of note, pyrexia experienced with targeted therapy is often better tolerated compared with pyrexia observed with chemotherapy, as they have different causes [30]. Pyrexia associated with targeted therapies, such as BRAF inhibitors, is possibly due to inflammation triggered by the inhibitor, whereas pyrexia associated with chemotherapy is largely due to neutropenic sepsis, where an infection is producing the fever [30]. Therefore, uncomplicated pyrexia in patients treated with targeted therapy is often well managed and, without complicating factors or sepsis, patients manage the fever at home with paracetamol, steroids and/or temporary dose interruption [30]. However, it is still important that patients experiencing pyrexia call the hotline team or designated local 24/7 number and are triaged as necessary to avoid missing sepsis.

Practical recommendations and supportive care measures

For patients with chronic but tolerable diarrhoea, dietary modifications are advised included eating small and frequent meals, introduction of a 'BRAT' diet (bananas, rice, apples and toast) and stopping lactose-containing products. Treatment with the anti-diarrheal loperamide can also be considered [30, 43]. For pyrexia, oral antibiotics and IV fluids can be administered as needed. Paracetamol can be administered with cautio We are contradicting ourselves here as we state in the above paragraph that patients can be managed with Paracetamol n but it may mask sepsis [30]. For general adverse events, advise patients to drink plenty of fluids, eat healthily, exercise regularly if possible and rest. Pain relief can be used as appropriate [43].

Patient and caregiver education

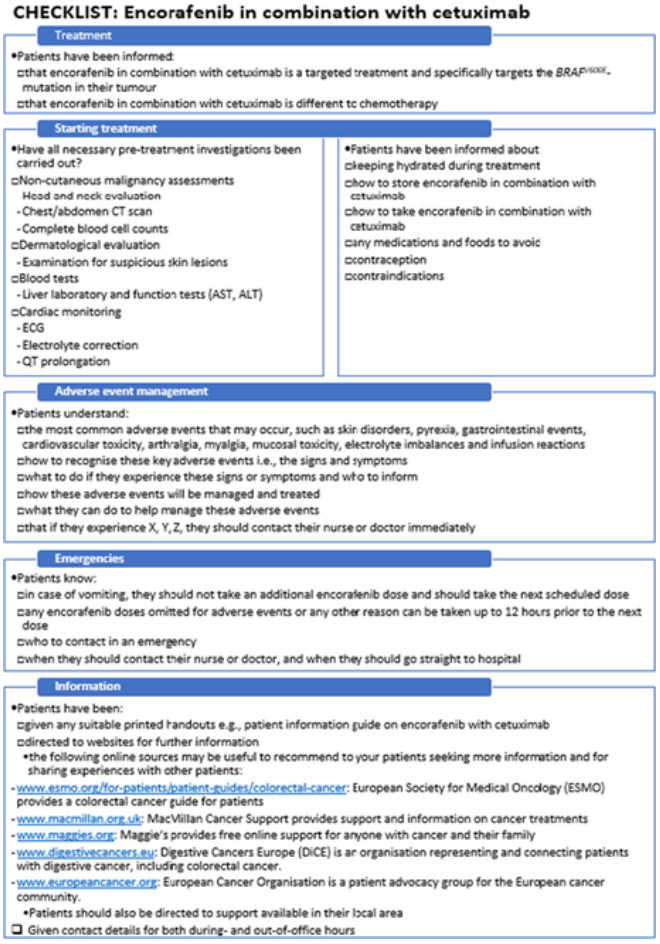
Education has become an important part of nursing care and involves counselling, informing and training patients [57]. Nurses have a role in educating patients and their caregivers on the disease and treatments they are receiving and possible adverse events. When switching to encorafenib in combination with cetuximab after prior systemic therapy, patients may have many questions and concerns. Nurses play a pivotal role in mitigating concerns and providing education on this treatment and its differentiation from other therapies. Patients may have previously received or be aware of chemotherapy and immunotherapy and nurses should be prepared to discuss how targeted therapy differs, including efficacy profiles, adverse event profiles and administration routes.

Patients also need to be aware of possible adverse events with encorafenib in combination with cetuximab, including signs and symptoms, to identify such events for efficient and effective management. Patients should also understand preventative measures and adverse events management, should these adverse events arise. Patients and their primary caregivers must be made aware of contacts for advice on adverse events and when to go to the hospital. Often, this is a hospital hotline providing a 24-h nurse-led telephone service.

The COVID-19 pandemic has exemplified how circumstances can make it difficult to reach patients and caregivers, so equipping patients and caregivers with the right information upfront is crucial. Increased patient education will contribute to efficient identification of adverse events and their timely management, leading to an improved quality of life, increased adherence to treatment and, therefore, maximal treatment benefits. Checklists that nurses can go through with patients would implement a formalised process ensuring patients are receiving all the correct information in a timely manner. A checklist could also improve confidence for both nurses and patients that processes for preventing and managing adverse events are completed accurately and thoroughly. Figure 4 shows an example checklist specifically for nurses and their patients with *BRAF*^{V600E}-mutant mCRC being treated with encorafenib in combination with cetuximab.

Fig. 4

Checklist for nurses and their patients with BRAF^{V600E}-mutant mCRC being treated with encorafenib in combination with cetuximab. *ALT alanine aminotransferase increase*, *AST aspartate aminotransferase increase*, *BRAF B-Raf proto-oncogene serine/threonine-protein kinase*, *CT computed tomography*, *ECG electrocardiogram*



Conclusions

Nu AQ5 rses play an important role in managing and caring for patients with *BRAF*^{V600E}-mutant mCRC. Nurses are pivotal in the prevention, early and efficient identification and subsequent management of treatment-related adverse events. This increases adherence to treatment by enabling patients to remain on treatment at the most optimal doses and duration, therefore maximising the treatment benefit and outcomes. An important part of the efficient identification and management of adverse events is the education of patients and their caregivers, which nurses can provide during the day-to-day management of patients. With efficient identification,

management or even prevention of adverse events, patients should be able to remain on encorafenib in combination with cetuximab and obtain maximal treatment benefits.

Publisher's note

Acknowledgements

Medical writing support was provided by Paige Johnson and Danielle Walsh of Meditech Media and Chrysalis Medical Communications, both part of Nucleus Global Ltd., and was funded by Pierre Fabre. The authors were responsible for all content and editorial decisions.

Author contribution

The authors were responsible for all content and editorial decisions. All authors were involved in material preparation, writing, reviewing, editing and conceptualization of the manuscript. All authors reviewed and commented on each version of the manuscript. All authors read and approved the final version of the manuscript.

Funding

Medical writing support was provided by Paige Johnson and Danielle Walsh of Meditech Media and Chrysalis Medical Communications, both part of Nucleus Global Ltd, and was funded by Pierre Fabre. The authors were responsible for all content and editorial decisions. The authors received no payment for the development of this manuscript. Pierre Fabre checked the manuscript for scientific accuracy only.

Declarations

Ethics approval This manuscript does not report a scientific study; therefore, no ethics approval is required.

Consent to participate This manuscript does not report a scientific study; therefore, no informed consent was obtained.

Consent for publication The authors affirm that their patients provided informed consent for publication of the patient images in Fig. 2c.

Competing interests Mathew Fowler (corresponding author) was an advisory board member for Vygon and received honoraria from Sanofi. Helene Tobback, Alice Karuri and Paz Fernandez–Ortega have no relevant financial or non-financial interests to disclose.

Supplementary information

ESM 1

Grading of key adverse events: National Cancer Institute Common Terminology Criteria for Adverse Events [54]

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