03/12/2018

RE: Removal of NHS England treatment break policy for cetuximab and panitumumab

We are writing to express our concern and call for the removal of the current six week treatment break policy imposed on EGFRi drugs, cetuximab and panitumumab, for their use in the first-line treatment of patients who have RAS wild type metastatic colorectal cancer (mCRC). Both cetuximab and panitumumab were approved for routine use on the NHS in England and Wales by NICE in July 2017 (TA439) for this indication. However, both drugs still appear on the Cancer Drugs Fund (CDF) list with the BlueTeq approval criteria stating:

"No treatment breaks of more than 6 weeks beyond the expected cycle length are allowed (to allow any toxicity of current therapy to settle or in the case of intercurrent co-morbidities)".

We have estimated based on data[i] that approximately 2,000 patients annually would benefit from a treatment break if offered. Furthermore, it is unclear what the rationale, reasoning and evidence base is for the treatment break policy. This restriction is not reflected in NICE TA439, has not been applied in Wales, Scotland and Northern Ireland, and correspondence from Carole Longson (then NICE Director of the Centre for Health Technology Evaluation) in April 2017 to oncologists on Bowel Cancer UK's Medical Advisory Board confirms that intermittent use of EGFRi is permitted within TA439:

"The feedback on your query about intermittent treatment with EGFRi in first-line treatment of CRC has come back from the Technology Appraisals team. Their response is that this is not excluded by the new guidance recommendation. The recommendation is for 1st line treatment, so as long as this is referring to continuing 1st line treatment (rather than moving to second line) then it would be covered by the guidance".

This treatment break policy is creating uncertainty and confusion amongst both the medical and patient community. In particular, both medical professionals and patients have expressed confusion over what constitutes a legitimate treatment break. We understand from NHS England's Specialised Services Treatment Break Circular that treatment breaks are permitted where a patient requires other interventions that preclude the use of chemotherapy, including surgery. However, the period of six weeks does not account for any potential delays in the pathway that can occur before surgery (i.e. delays in receiving scans) and had led to many uncertainties around reinstating funding following an extension to the break. In one case, an oncologist has had to re-commence treatment for cetuximab following delays to surgery (Annex A).

This restriction imposed by NHS England appears to be completely arbitrary, which only serves to restrict a clinician's ability to make sound clinical judgements and to treat patients according to their individual needs and preferences.

There is also no medical basis for the six-week treatment break policy, with a number of Phase II and III studies demonstrating that patients are able to take treatment breaks safely. These include:

- The UK phase III COIN trial[ii] which explored treatment breaks in the setting of mCRC. This study recruited 1630 patients and demonstrated no detriment in overall survival. In addition, the trial found an improvement in quality of life, lower toxicity and three months less drug use and resulting cost savings. Patients, on average, could safely stop treatment for three months or more, with a significant proportion of patients not needing to restart treatment for 9-12 months.
- Phase II studies such as COIN B[iii] have not demonstrated a survival advantage when comparing the continuous use of cetuximab versus intermittent use.
- International phase III studies (CAIRO3[iv] and AIO0207[v]) using alternative biological agents i.e. bevacizumab whose SmPC also indicate continuous use, have demonstrated no overall survival advantage for continuous bevacizumab therapy versus intermittent use even when data from these two large phase III trials is combined[vi].

Furthermore, treatment breaks are vital to improving a patient's quality of life. This is because the prolonged use of cetuximab and panitumumab causes toxicities to accumulate and worsen. **Unfortunately, due to the lack of clarity and transparency of NHS England's treatment break policy, many patients feel forced to remain on continuous treatment.** Patients fear any break will result in a withdrawal of their treatment funding (Annex C). As a consequence, we have anecdotal evidence of patients having up to 70 cycles of treatment every two weeks without any breaks to recover from toxicities. It is clear that, at a time when patients have limited choice and the management of metastatic cancer is taking over much of their lives, this policy restricts one of the few things they can have control over; choosing the best treatment options for them and how to achieve the best quality of life possible.

Bowel Cancer UK has heard from a number of patients who are experiencing painful side effects as a result of this restriction, impairing their day-to-day activities and significantly affecting their quality of life (Annex B). This is extremely important when the median survival of mCRC patients is 24-30 months.

Key side-effects experienced by patients include:

- Extremely painful red skin rashes;
- Dry and peeling skin across hands, feet and face;
- Cystic, painful acne-like spots;
- Nausea;
- Diarrhoea;
- Reduced appetite.

Patients have also emphasised the psychological impact continued treatment has had. Many patients have described how their side-effects have left them feeling debilitated, isolated and self-conscious. In addition, the treatment break policy has restricted them from attempting to return to any level of 'normality', where they are unable to return to work or take extended holidays with family.

In circumstances where patients have had their treatment withdrawn due to taking a break, many have been left struggling to self-fund for further delivery of their EGFRi medication. This creates variation in access and also restricts patients from accessing vital life-prolonging and potentially life-saving medication. Furthermore, this causes patients and their family's unnecessary stress at a time when they are already going through an extremely difficult time coping with a life-limiting cancer diagnosis.

In addition, by restricting the length of time a patient is able to take a break, **NHS England's treatment break policy is only serving to add additional costs and pressure on the NHS.** We estimate that the ICER per QALY for the continuous use of cetuximab or panitumumab versus intermitted use is in the region of £500,000. In addition, by forcing patients to remain on continued treatment, patients spend more time at hospital to receive their fortnightly treatment and receive more district nurse visits prior to each clinic. **Patients are also prescribed a multitude of additional NHS-funded medications to cope with the additional side effects.** These prescriptions include: long-term antibiotics for their skin; medication for gastric irritation and chronic diarrhoea, steroid creams and emollients, and GCSF treatment to prevent patients from becoming neutropenic.

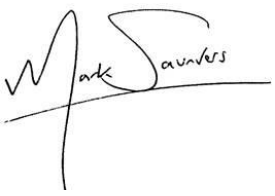
It is therefore imperative that once NICE has approved cancer drugs for routine use on the NHS, no further restrictions for use are added by NHS England through the CDF. Patients have a right enshrined in the NHS Constitution to access drugs approved for use by NICE. This restriction denies patients this basic right and has added an unnecessary barrier for patients who already have very limited treatment options available.

We urge NHS England to remove the six-week treatment break policy imposed on cetuximab and panitumumab and prevent further restrictions from being added to cancer drugs that restrict life-prolonging and potentially life-saving medication from patients.

Yours Sincerely,

Deborah Alsina MBE,
CEO of Bowel Cancer UK

Professor Mark Saunders
Consultant Clinical Oncologist, The Christie NHS
Joint Chair of Bowel Cancer UK Medical Advisory Board



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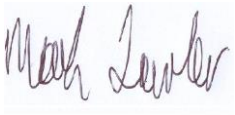
Dean of Education and Chair in Translational Cancer Genomics



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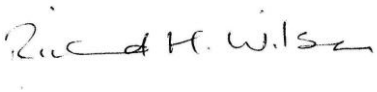

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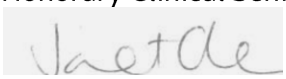

Professor Richard Adams
Professor of Clinical Oncology and Honorary Consultant,
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Appendices

Annex A: Bowel Cancer UK forum post, 9th June 2018 written by patient's wife.

User1 relative 9th June

"He was due to have liver and lung resections in March and had to stop Folfiri/Cetuximab 6 weeks before to clear the chemo before the liver operation. Giving up Cetuximab was a very hard decision he had to make in order to get the liver resection.
We then had a very stressful time trying to deal with 4 hospitals trying to get them to talk to each other concerning CT timing/results. The last thing our Oncologist said when he stopped chemotherapy and had the picc line taken out was if for any reason your liver operation is delayed or cancelled, let me know. He said I'm not letting you lose Cetuximab AND not have a resection.
We finally managed to get the CT's done but to be sure they needed a liver MRI. They were working on getting all the results just before the operations but we needed the results in time to go back onto Cetuximab before the 6 week limit it was very, very stressful.
In the end it got to 5 weeks and the Oncologist said he couldn't wait any longer and straight away he had a new picc line and Cetuximab restarted which shocked the liver team at the other hospital as they had still been working on the original surgery date which would now have to be postponed.
Finally all the scan results came in and everything had shrunk so much that it was not visible/too small to operate on. So our Oncologist had done the right thing to keep the funding

for us but it was a very stressful time and a close call.
All the best".

Annex B: Jane, mCRC patient, discusses the impact of the treatment break policy on her quality of life

I was initially diagnosed with stage 1 bowel cancer in January 2016, aged 43. Further investigations in October 2016 revealed a second primary bowel cancer at stage 3. Following three extensive surgeries, a diagnosis of Lynch syndrome, and 6 months of adjuvant chemo-therapy, in November 2017 the devastating news came that the cancer had spread throughout my lymph system, liver, bones and an adrenal lesion. A diagnosis of Stage 4 aggressive cancer was a complete shock and it came with a very poor prognosis.

In December 2017, treatment was commenced with chemotherapy (FOLFIRI) and a biological targeted therapy - panitumumab. Despite a rocky start with severe side effects of diarrhoea, abdominal pains, fatigue, severe neutropenia and skin rash, 6 cycles were completed with a dose titration. A CT scan concluded a phenomenal response with marked regression of multiple tumours in the liver. The bones had become sclerotic, the lymph system had improved and the adrenal lesion had completely disappeared. Following another 6 cycles my disease was stable with ongoing response.

In June 2018, my oncologist's advice and opinion was that a treatment break would be safe and beneficial physically, psychologically and for my wellbeing. The 6 week treatment break policy imposed on panitumumab would not allow this. If I took the longer break that my body would benefit from to allow some recovery and resilience for further treatment, I would not be able to have this drug again unless I paid privately.

My oncologist is equally frustrated as clinical evidence has shown that a treatment break would not have an overall impact. He is not able to treat me and my cancer as an individual and has to be controlled by arbitrary rules and guidelines that make little sense. Therefore we made the decision to continue with treatment omitting one chemotherapy drug. However, panitumumab cannot be prescribed as a monotherapy under current guidelines, so I now have one chemo-therapy alongside panitumumab. I am too scared to risk a break off treatment and lose the funding for a drug that I have responded so well to.

A further CT scan in October 2018 reports stable disease and ongoing response. Once again, I cannot risk having a treatment break, because of the arbitrary funding rule. However, the impact and side effects of long term chemotherapy and biological therapy are grueling.

The physical side effects of this treatment cause me to have:

- Skin problems including a skin rash, pustules, redness to the face, dry and cracked skin, and paronychia that at times is severe and painful;
- Problems with my vision and sore eyes;
- Hair thinning and strange hair growth also;
- Effects on the gastrointestinal tract including severe diarrhoea, abdominal pain, stomatitis and other related complications;

- Every cycle of treatment, I suffer with cystitis that can be very painful;
- Nausea and poor appetite are affected. At times food tastes of nothing.
- I always feel fatigued;

In addition, to combat neutropenia I have to inject for 7 days out of the 14 day cycle to stimulate my bone marrow to make white bloods cells.

The psychological side effects of long-term chemotherapy are just as difficult. The physical skin effects have knocked my confidence, self-esteem and at times stop me going out. Long term antibiotics to control the skin effects along with the chemotherapy and biological therapy do not allow me to be in the sun. Any sun exposure exacerbates my skin tenfold. Who wants to stay indoors on a beautiful sunny day? Severe diarrhoea keeps me at home. It's always a worry when going somewhere. I love to eat out but often when I get there I feel nauseous and have no appetite. It is also very difficult to plan trips and almost impossible to book any holidays within a 14 day cycle (3 of those 14 days you are receiving chemotherapy). Due to the high demand at my oncology center, there is no flexibility to move treatment days to allow life events to continue.

A treatment break would increase capacity at my chemotherapy suite, consultant time for pre-assessment appointments, district nurse care, and would reduce the number of blood tests required pre-chemotherapy. In addition, my ongoing treatment does not allow me the opportunity to return to my job in the NHS as a Lead Nurse and Clinical Specialist. A longer treatment break could allow me to return to work for the NHS and once again contribute as I have done all my career. All these things have a huge impact on not just me, but my partner, family and friends.

Despite all this, I am of course thrilled at the response that I am having with my treatment and am for-ever grateful. However, taking a longer treatment break would allow my body and mind to recover for a period of time and allow me to withstand further treatment. It would also lower the amount of additional drugs I am prescribed to counteract my side effects from ongoing treatment. Taking the break my body needs should not lead me to fear that I can't access my medication again, and my quality of life should not be governed by 'guidelines'. A treatment break would allow some normality back into my life and for so many others who are living with stage 4 bowel cancer.

Jane Ashford

RGN, DipHE in Health Studies, BSc Honours Nursing, Non-Medical Prescriber.

Annex C: Bowel Cancer UK forum posts, 19th June 2018, conversation between two patients.

User 2 patient 19th June

"Hi. Thank you for your reply, info and tips! You have both gone through so much. I am on cycle 12 tomorrow of FOLFIRI and Panitumumab. CT in a few weeks. As discussed before, I am concerned about the funding as I have no more treatment booked after tomorrow and still no appointment with my oncologist.... eek 😖! I too have had a bad skin reaction last cycle... had to stop Doxycycline so that's probably why it was so bad. I think you can just have 5Fu with Cetuximab/ Panitumumab, reading the NHS Cancer Drug Fund document... however,

what confused me even more was my oncologist suggested he might just keep me on Panitumumab... I haven't come across anyone just having a biological drug alone. Good luck to your husband with treatment tomorrow and scan results."

User 3 relative 19th June

"In that case you need to sort it out tomorrow!!

Don't leave the unit without new chemotherapy/Panitumumab appointments to give you enough time to have your scan and get the results. Tie yourself to the 'machine that goes beep' with plastic infusion tubing if you have to 😀.

It's not worth the chance of losing funding if you still need it. You need to at least speak to the oncologist's secretary and put your case to him/her and get some action.

I hope your skin is calming down now and all goes well tomorrow."

User 2 patient 19th June

"Thank you for the push...
I will phone the secretary first thing and speak to the chemotherapy nurses when I get to the unit. If it wasn't for this forum and your posts I wouldn't have even known about the funding issue! Skin is better thanks...
Until we go again!!!!"

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