DRAFT FOR PUBLIC CONSULTATION

Clinical Commissioning Policy Proposition:

Chemosaturation for liver metastases from ocular melanomas

Reference: NHS England A02X05/01

Information Reader Box (IRB) to be inserted on inside front cover for documents of 6 pages and over, with Publications Gateway reference number assigned after it has been cleared by the Publications Gateway Team. Publications Gateway guidance and the IRB can be found on the Intranet.

Clinical Commissioning Policy Proposition: Chemosaturation for liver metastases from ocular melanomas

First published: March 2016

Prepared by NHS England Specialised Services Clinical Reference Group for **Hepatobiliary**

Published by NHS England, in electronic format only.

Classification: OFFICIAL

Contents

Equality Statement

NHS England has a duty to have regard to the need to reduce health inequalities in access to health services and health outcomes achieved as enshrined in the Health and Social Care Act 2012. NHS England is committed to fulfilling this duty as to equality of access and to avoiding unlawful discrimination on the grounds of age, gender, disability (including learning disability), gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, gender or sexual orientation. In carrying out its functions, NHS England will have due regard to the different needs of protected equality groups, in line with the Equality Act 2010. This document is compliant with the NHS Constitution and the Human Rights Act 1998. This applies to all activities for which NHS England is responsible, including policy development, review and implementation.

Plain Language Summary

Ocular melanoma is a rare form of eye cancer which most commonly spreads to the liver. Ocular melanoma can be uveal or conjunctival depending in which part of the eye it originated. Conjunctival melanoma typically spreads around the body differently and is therefore not relevant to this policy. When localised just to the eye, there are various treatment options available, but once spread around the body, the prognosis is poor and life expectancy is significantly reduced.

Spread of the cancer cells to the liver, known as metastases, occurs in up to half of all ocular melanoma patients. At this stage, there are limited treatment options as liver cancer is not normally able to be removed surgically. In addition, systemic chemotherapy (strong cancer-destroying medication delivered to the entire body) is not well tolerated and is not proven to be effective.

Chemosaturation is a method of delivering the strong chemotherapy medications directly to the liver, bypassing the rest of the body and avoiding the toxic effects.

NHS England has concluded that there is not sufficient evidence to support a proposal for the routine commissioning of chemosaturation for the treatment of liver metastases from ocular melanoma primary cancers.

1. Introduction

This document describes the evidence that has been considered by NHS England in formulating a proposal to not routinely commission chemosaturation for liver metastases.

For the purpose of consultation NHS England invites views on the evidence and other information that has been taken into account as described in this policy proposition.

A final decision as to whether chemosaturation for hepatic metastates will be routinely commissioned is planned to be made by NHS England by June 2016 following a recommendation from the Clinical Priorities Advisory Group.

2. Proposed Intervention and Clinical Indication

Ocular melanoma (OM) is a rare cancer of the eye predominantly affecting the uvea but on occasion, the conjunctiva. In the UK, between 500 - 600 patients are diagnosed with uveal melanoma each year (Macmillan Cancer Support, 2014). Approximately 50% of patients with uveal melanoma will develop metastatic disease within five to ten years of their initial diagnosis. Typically these are liver metastases, at which point it is deemed incurable (Agarwala S. et al, 2014).

If the melanoma is localised (i.e. has not metastasised), there are various treatments that may be considered including radiotherapy, surgery, cryotherapy, transpupillary thermotherapy, chemotherapy eye drops and photodynamic therapy. If metastases are detected early, there are interventions that potentially extend life expectancy and improve quality of life for those affected. These include surgical resection, thermal ablation, systemic chemotherapy, elective internal radiation therapy (SIRT) and trans-arterial chemoembolisation (TACE) however many of these will not be suitable or tolerated.

Chemosaturation therapy is a new method of treating cancers in the liver; both primary hepatic cancers and liver metastases. This approach allows for very high concentrations of a chemotherapeutic agent (melphalan) to be administered directly to the liver in isolation, and then, via haemofiltration, cleared from blood to achieve negligible levels in the systemic circulation avoiding systemic toxicity. Chemosaturation is not currently funded by NHS England and is only recommended by NICE within the context of research. In trials, chemosaturation therapy has been primarily directed at liver only metastases for melanoma and ocular melanoma, not treatable with resection. The rationale for this is that these are particularly hyper vascular tumours, which often present with diffuse liver metastases that are resistant to other existing treatments and have a very poor prognosis.

Currently, if surgical resection is not possible, then many patients are offered systemic chemotherapy (dacarbazine). Dacarbazine commonly results in systemic toxicities including neutropenia, nausea and fatigue together with a low limited disease response rate (<5%). However there is no evidence that this agent provides any extension of overall survival in any form of melanoma; or indeed any meaningful disease control.

3. Definitions

Ocular melanoma (OM):
A rare form of eye cancer that affects between 580 - 700 people in the UK each year. Uveal melanoma is the most common with approximately 500 - 600 new diagnoses in the UK each year (Macmillan Cancer Support, 2014). Conjunctival melanoma affects approximately 80 -100 people each year, but is typically associated with a different spread of metastatic disease and therefore chemosaturation is not frequently indicated. There are numerous treatments for uveal melanoma whilst it is still isolated within the eye however between 30-50% of patients will have a recurrence of the cancer within 5-10 years of diagnosis, often associated with metastasis. Ocular melanomas typically metastasise to the liver and are associated with a median survival of four to six months (Agarwala S. et al, 2014).

Surgical resection involves the removal of tumours by surgical technique, both laparoscopic and open surgery. Liver metastases are rarely suitable for surgical resection due to their locations and the presence of microtumours.

Systemic chemotherapy: Dacarbazine is the standard first-line chemotherapeutic agent used systemically for liver metastases secondary to ocular melanoma. It has a low response rate (clinicians estimate approximately 5%) and is usually not tolerated.

Hepatic chemosaturation uses a minimally invasive fluoroscopic guided technique that avoids some of the major complications associated with open isolated hepatic perfusion techniques. Isolating the liver allows for a higher concentration of chemotherapeutic agent to be delivered locally than can be given systemically as normal liver tissue is much more tolerant of high dose melphalan than other organs such as the kidneys or bone marrow. Hepatic chemosaturation treats both visualised and non-visualised micro tumours in the liver while minimising the systemic toxicity. The procedure may be repeated on a patient due to the minimally invasive techniques used. It has been shown to slow down or reverse the progression of tumours from certain cancers in the liver. Liver metastases derive the majority of their blood supply from the hepatic artery and a minimal amount from the portal vein. The concept of regional chemotherapy utilises this physiology, using catheter directed techniques to deliver intra-arterial chemotherapy directly to the liver lesions (both those visible and those too small to identify). Chemosaturation is not a curative treatment, but is intended to prolong life and improve quality of life (OcuMel UK, 2015).

4. Aim and Objectives

This policy proposition aims to define NHS England's commissioning position on chemosaturation as part of the treatment pathway for adult patients with liver metastasis of occular melanoma primary.

The objective is to ensure evidence based commissioning with the aim of improving outcomes for adults with liver metastasis of occular melanoma primary.

5. Epidemiology and Needs Assessment

It is estimated that between 500 - 600 people are diagnosed with uveal melanoma in the United Kingdom each year, representing approximately 420 - 500 people across England alone (Macmillan Cancer Support, 2014). As conjunctival melanoma, estimated at below 80 new patients in England each year, is typically associated with a different pattern of disease rarely metastasising to the liver only and thus chemosaturation is not an optimal therapy. Therefore this policy concerns the use of chemosaturation for liver metastases from uveal melanoma only. Of the 420 - 500 uveal melanoma patients in England each year, between 30-50% of patients (approximately 210 - 250 people) will suffer a recurrence of their cancer within 5-10 years of initial diagnosis, typically associated with metastatic liver disease (Agarwala S. et al, 2014). Of these patients, 90% will have liver involvement of their melanoma, however 70% (approximately 150 - 175 people) are likely to have metastasis isolated purely to the liver (Ocular Melanoma Foundation, 2015).

Of this patient cohort, clinicians have estimated that between five and seven patients may be suitable for surgical resection, one or two patients suitable for thermal ablative therapy and another one or two patients suitable for chemoembolisation. The patient cohort for whom chemosaturation could be considered is required to by reasonably fit and have a disease burden less than 60% (i.e. metastases are involving less than 60% of the liver) without significant liver failure. Exclusion criteria include significant cardiac or respiratory disease and any anticoagulant pathologies that increase the risk of bleeding. In addition, metastases to the brain and abnormal liver anatomy would also exclude a patient from chemosaturation suitability. Clinicians estimate that 50-75 patients per year will be suitable for chemosaturation.

6. Evidence Base

NHS England has concluded that there is not sufficient evidence to support a proposal for the routine commissioning of this chemosaturation for the liver metastases from ocular melanoma primaries.

In the current review we searched for relevant articles from 2005 onwards. No systematic reviews, meta-analyses or randomised controlled trials were identified. Two case series studies met the inclusion criteria. Both the studies included mixed population with very small number of ocular melanoma patients. No studies were found that had a control group. One evidence review to support NICE guidance (search date 2013) on the treatment of primary and metastatic liver cancer was identified. It included five case series, of which one provided evidence on efficacy in ocular melanoma specifically. All studies were of poor quality thus there is insufficient evidence to draw firm conclusions.

In a prospective case series study (n=28, 10 ocular melanoma patients) included by the NICE review, 20% (2/10) of treated patients were observed to achieve complete response, 30% (3/10) were observed to achieve partial response and 30% (3/10) were observed to achieve minor response to the intervention.

In a subsequent retrospective case series, percutaneous hepatic perfusion was evaluated in a total of 14 patients which included eight ocular melanoma patients. Out of the eight ocular melanoma patients, three presented partial response and three showed stable

disease; the response status of the other two patients was not reported.

In a third retrospective case series, total of 10 patients were included out of which five were ocular melanoma patients. The total median percentage decrease in hepatic tumour volume in the patients who had stable disease or partial response was 48.6% for those with ocular melanoma.

Hepatic progression free survival period in this study was about 7.6 months for ocular melanoma patients. Median overall survival ranged from 10 months to about 3.9 years. As this study did not have a control group, it is difficult to assess whether this represents an improvement in expected outcome. The Ocular Melanoma Foundation in the US reports that without treatment median survival is two to eight months for people with metastatic ocular melanoma, but the original source of this estimate was not cited. One case series (n=119) reported that those who had systemic chemotherapy had a median survival of 9.5 months, while those who had surgery or intrahepatic chemotherapy (local treatment) had median survival of 32.4 months. However, caution should be applied when comparing the figures from these sources with those from the included case series, as the populations may not have been comparable and the sample in the included study was very small (n=5).

Overall, previous studies have reported nine months median overall survival for patients with liver cancer from ocular melanoma. Another study that assessed the course and outcome of metastatic uveal melanoma reported that, patients who received a particularly improved survival (median, 32.4 months), compared with patients who received systemic chemotherapy (median survival, 9.5 months).

In the case series included in the rapid evidence review conducted by NICE in 2013 (five case series, only two included ocular melanoma patients, n=243) and the subsequent case series, between 3.1% and 7.1% of the patients having the procedure died due to adverse events. These events included ruptured hepatic artery leading to gastrointestinal haemorrhage, gastric perforation, hepatic failure (this patient's liver was 90% tumour), and streptococcal sepsis, neutropenia, spontaneous retroperitoneal haemorrhage within 24 hours of the intervention and retroperitoneal giant hematoma 30 hours after the intervention.

The largest case series in the NICE review (n=121) reported that 13% of patients had haemorrhage, 7% of which were grade 3 or 4 events. There were two intracranial haemorrhages in patients with brain metastases, and one of these patients died. This case series also reported 11% of patients had grade 3 or 4 gastrointestinal events, 17% had grade 3 or 4 cardiovascular events, and 44% had hepatic events.

Some of the other reported adverse events included bone marrow suppression, leading to cases of pancytopenia, leukopenia, anemia, and neutropenia.

Conclusions

We found very limited evidence on the effectiveness of percutaneous hepatic perfusion procedure. The included studies were small and lacked control groups. No studies were identified of high quality to draw firm conclusions on the effectiveness of the procedure in patients with liver metastasis from ocular melanoma.

We found very limited evidence on the safety of percutaneous hepatic perfusion procedure. No studies were identified of high quality to draw firm conclusions on the safety of the procedure in patients with liver metastasis from ocular melanoma.

No cost-effectiveness studies were identified to comment on the cost-effectiveness of this procedure.

7. Documents That Have Informed This Policy Proposition

None.

8. Date of Review

This document will lapse upon publication by NHS England of a clinical commissioning policy for the proposed intervention that confirms whether it is routinely or non-routinely commissioned (expected by June 2016)