

Clinical Commissioning Policy: Chemosaturation for liver metastases from ocular melanomas

Reference: NHS England: 16014/P



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Medical	Operations and Information	Specialised Commissioning
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Publications Gateway Reference: 05527s

Document Purpose	Policy
Document Name	Clinical Commissioning Policy 16014/P
Author	Specialised Commissioning Team
Publication Date	13 July 2016
Target Audience	CCG Clinical Leaders, Care Trust CEs, Foundation Trust CEs , Medical Directors, Directors of PH, Directors of Nursing, NHS England Regional Directors, NHS England Directors of Commissioning Operations, Directors of Finance, NHS Trust CEs

Additional Circulation List

Description Not Routinely Commissioned - NHS England will not routinely commission this specialised treatment in accordance with the criteria described in this policy.

Cross Reference This document is part of a suite of policies with Gateway Reference 05527s.

Superseded Docs (if applicable) N/A

Action Required N/A

Timing / Deadlines (if applicable) N/A

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Document Status

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Clinical Commissioning Policy: Chemosaturation for liver metastases from ocular melanomas

First published: July 2016

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

Published by NHS England, in electronic format only.

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Policy Statement

NHS England will not routinely commission chemosaturation for liver metastases from ocular melanomas in accordance with the criteria outlined in this document.

In creating this policy NHS England has reviewed this clinical condition and the options for its treatment. It has considered the place of this treatment in current clinical practice, whether scientific research has shown the treatment to be of benefit to patients, (including how any benefit is balanced against possible risks) and whether its use represents the best use of NHS resources.

This policy document outlines the arrangements for funding of this treatment for the population in England.

Equality Statement

Promoting equality and addressing health inequalities are at the heart of NHS England's values. Throughout the development of the policies and processes cited in this document, we have:

- Given due regard to the need to eliminate discrimination, harassment and victimisation, to advance equality of opportunity, and to foster good relations between people who share a relevant protected characteristic (as cited under the Equality Act 2010) and those who do not share it; and
- Given regard to the need to reduce inequalities between patients in access to, and outcomes from healthcare services and to ensure services are provided in an integrated way where this might reduce health inequalities

Plain Language Summary

About ocular melanoma

Ocular melanoma is a rare form of eye cancer. When the cancer stays just in the eye, there are a number of treatments. However, once it spreads around the body, how long the patient will live is much less.

Ocular melanoma can affect two parts of the eye:

- It usually affects the **uvea** – the middle layer of the outside of the eye. This type of cancer spreads to the liver in up to half of patients. This can be treated with 'chemosaturation' and so is covered by this policy.

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- It can also affect the **conjunctiva** – this is on the inside of the eyelids and covers the white part of the eye. This cancer spreads around the body differently and so is not considered within this policy.

About current treatments

When cancer cells spread to other parts of the body, these are called 'metastases'. At the moment there are limited ways to treat the spread to the liver. This is because cancer in the liver cannot normally be removed by surgery. Also, giving strong cancer medicines ('systemic chemotherapy') to the whole body causes serious side effects - and we are not sure if it is effective.

About the new treatment

The new treatment is called 'chemosaturation'. This is a way of getting the strong chemotherapy medicines directly to the liver. This means it does not affect the rest of the body - and so there are fewer side effects.

What we have decided

NHS England has looked at the proposal to treat liver metastases from ocular melanoma cancer with chemosaturation. We have decided that there is not enough evidence to support this proposal to make the treatment available.

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 arising from ocular melanomas.

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 and trans-arterial chemoembolisation 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 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.

2 Definitions

Ocular melanoma (OM) is a rare form of eye cancer that presents in two forms: uveal and conjunctival. Uveal melanoma is the most common. Conjunctival melanoma affects fewer patients and typically associated with a different spread of metastatic disease and therefore chemosaturations is not frequently indicated.

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 up to 5%) and is usually not tolerated.

Hepatic chemosaturations 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 chemosaturations 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). Chemosaturations is not a curative treatment, but is intended to prolong life and improve quality of life (Ocumel UK 2015)

3 Aims 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 ocular melanoma primary.

The objective is to ensure evidence based commissioning in the use of chemosaturation for adults with liver metastasis of ocular melanoma primary.

4 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 those who are 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. On this

basis, clinicians estimate that 50-75 patients per year could be suitable for chemosaturation.

5 Evidence Base

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

In the current review relevant articles from 2005 onwards were searched for. 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 (NICE, 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, anaemia, and neutropenia.

Conclusions

Very limited evidence of effectiveness was found for 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.

Very limited evidence was found 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.

6 Documents which have informed this Policy

Not applicable.

7 Date of Review

This document will be reviewed when information is received which indicates that the policy requires revision.

References

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