METASTATIC UVEAL MELANOMA: DIAGNOSIS AND TREATMENT. A LITERATURE REVIEW

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ABSTRACT

In the past three decades many efforts were done to improve the visual prognosis of patients with uveal melanoma. However, mortality has remained unchanged. The systemic prognosis depends on the size and other characteristics of the lesion. It is not affected by the choice of local treatment. This suggests dissemination at an early stage. The failure to improve survival is caused by difficulties in early detection of metastases and the limited susceptibility of these metastases to systemic therapies.

RÉSUMÉ

Les trente dernières années, différentes approches thérapeutiques ont amélioré le pronostic visuel des patients qui présentent un mélanome uvéal. Malheureusement, la mortalité n'a pas changé. Le pronostic vital dépend de l'étendue de la tumeur et de ses autres caractéristiques, et non du choix du traitement local. Il semble que des micro-métastases sont souvent déjà présentes au moment du diagnostic du mélanome. L'impossibilité d'améliorer la survie est liée aux difficultés de détecter les micro-métastases et à leur résistance aux traitements systémiques.

KEY-WORDS

Uveal melanoma, prognosis, treatment of metastases

MOTS-CLÉS

Mélanome uvéal, pronostic, traitement des métastases

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INTRODUCTION

Uveal melanoma is the most common primary intraocular malignancy, affecting 6 to 8 persons per million each year in the western world. Although less than 2% of patients show evidence of metastasis at presentation, over 40% of patients will die from widespread disease (6). This probably relates to early onset of, initially non-detectable, melanoma metastasis.
In this communication the literature on current detection and treatment modalities for metastatic uveal melanoma is reviewed.

MATERIALS AND METHODS

We used computerized search engines and information resources to find titles and abstracts of recent publications on the subject. These publications were reviewed and compared.

RESULTS

TREATMENT OF UVEAL MELANOMA:

During more than a century enucleation was considered as the standard treatment for all uveal melanomas. By the end of the seventy's some authors thought that enucleation might have an adverse effect on survival (29). The source of these ideas was the peak in death rate that was seen early after enucleation, in contrast to the low incidence of metastasis before treatment. Fluctuations in tissue pressure were thought to account for iatrogenic spread of tumour cells during the surgical procedure. Since only little is known about the natural course of uveal melanoma and its spread, this hypothesis was based on statistical extrapolations. It is contradicted by estimations on tumour doubling time. These rather indicate that patients who eventually show dissemination most probably already carry micrometastases at the initial diagnosis of the primary tumour (14,21,22). Despite this controversy it is still generally accepted that enucleation should be carried out with minimal manipulation. Moreover, these ideas were an impulse to search for alternative treatments. Especially as some enucleated eyes, diagnosed as malignant melanoma, contained no melanoma on histopathology (22). The need for a conservative, i.e. vision-sparing treatment evolved. Since then many trials were undertaken to evaluate these alternatives. Today we may consider follow-up, photocoagulation, transpupillary thermotherapy, brachytherapy, proton beam therapy or enucleation. Our choice of treatment will depend on the size and location of the tumour and the possibility for retaining some useful vision. We presently know that the various local treatments carry the same vital prognosis, if tumours of similar characteristics are compared (2,5,7). This supports the idea of early dissemination. If micrometastasis is already initially present, a local treatment, no matter how effective, will not cure the disease, as long as its not combined with a systemic therapy.

DETECTION OF METASTASIS:

Uveal melanomas predominantly disseminate to the liver in a haematogenous fashion (6). Detection of metastasis is therefore concentrated on this site. Screening programs that are routinely used, often include semi-annual liver function tests, abdominal ultrasonography and chest x-ray. A retrospective study compared the value of these various tests (15). In this study the sensitivity of the overall screening program is assumed to be 100%, and the relative sensitivity of the individual tests is compared. However, if one considers the possibility of subclinical metastasis, the absolute sensitivity of each test is very likely to be much lower, as suggested in later reports (17). Anyway, among the routinely used tests, abdominal ultrasonography is most valuable. Liver function tests, although more sensitive, are not specific enough, resulting in a poor positive predictive power. Chest X-ray has a very low yield, as one can expect from the small prevalence of lung metastasis as compared to liver metastasis. Chest X-ray is now often abandoned as a follow-up examination, but should be recommended in the initial workout to exclude the possibility that the uveal tumour is a metastasis of a primary lung carcinoma (13).
To overcome the problem of initially undetectable micro-metastasis some tried to detect small amounts of circulating melanoma cells. This

was done by detecting circulating tyrosinase mRNA, using Reverse Transcriptase and Polymerase Chain Reaction. It was indeed possible to demonstrate as few as 1-2 cells per ml blood (27). Unfortunately, later studies showed that this was not sufficiently sensitive to detect metastasis at an early stage (16). Currently, research is done on early detection of tumour cells in bone marrow, using immunomagnetic techniques (10).

PREDICTION OF PROGNOSIS:

Since we cannot detect metastasis at a very early stage, it might be more interesting to predict prognosis. In patients at high risk of developing metastasis, a (future) adjuvant therapy can be considered.

Clinical prognostic factors include tumour size, location of the tumour, extrascleral extension and patient age. Largest tumour diameter can be considered as the most important prognostic parameter. It has a strong correlation with prognosis and its measurement is easy and reproducible (23).

Histopathologic prognostic factors include Callender cell type, presence of vascular loops and other vascular patterns, mitotic rate and size and pleomorphism of nucleolar area. Assessment of these features is less reproducible and sometimes needs specialized equipment (23,24). Moreover, there is no tissue specimen available when neither enucleation nor fine needle aspiration biopsy were performed. In these cases ICG angiography and ultrasonography are sometimes used to visualize tissue microstructure (4,25).

On a molecular level there are numerous factors with a possible prognostic value. These include cytogenetic abnormalities, expression of cell adhesion molecules and presence of proteolytic enzymes and cytokines. Cytogenetic analysis of uveal melanoma revealed that monosomy of chromosome 3 and trisomy of chromosome 8q are associated with poor outcome. Deletions of chromosome 6q appear to be protective (8,28). For uveal melanoma research in the field of molecular biology has been limited. The exact role of expression of antigens, ezrins, integrins and others is still uncertain (11,12,20).

TREATMENT OF METASTATIC UVEAL MELANOMA:

Once the diagnosis of metastatic uveal melanoma is established, a survival of less than one year can be expected. So far, no systemic therapy has been particularly effective in increasing this survival (1). Some preliminary studies suggest a partial response to regimens of combined chemotherapy, including interferon alpha-2b (9,26). However, these therapies remain to be evaluated in randomised trials.

The median survival of patients who first develop liver metastasis is shorter than in patients who first develop metastasis at other sites, i.e. 7 months versus 18 months (18). This has led to the evaluation of regional hepatic therapies, such as intrahepatic arterial chemotherapy. A catheter connected to a subcutaneous access is implanted into the hepatic artery. Cisplatine or fotemustine are administered to the liver and might be combined with embolization with polyvinyl sponge. Response to these regional therapies might be better than those achieved with systemic chemotherapy, but the effect on survival remains limited (3,19). Responses are most often only partial and temporary and, once again, need to be evaluated in larger trials.

DISCUSSION

The efforts of the Collaborative Ocular Melanoma Study Group (COMS) and related studies have opened the way to evidence based guidelines for the local treatment of ocular melanoma (5,6,7). Today, we can offer our patients a better visual prognosis without impact on life expectancy. However, we should not be tempted to a false sense of security. Although screening for dissemination might often seem reassuring initially, over 40% of patients will be confronted with a diagnosis of metastasis, often only 2-4 years later. Detection of metastasis at an early stage seems a difficult if not impossible task. Nevertheless, controlling the disease at a micrometastatic stage offers the best prospects. An adjuvant therapy given at patients at risk might be ideal.

In order to identify patients at risk we need to be able to assess prognostic factors. Some factors are well established such as tumour size,

location and extrascleral extension. Some more factors have a definite prognostic value, but are not always accessible, such as cytogenic abnormalities (8, 28) and histological characteristics (23,24). Even more factors have a possible but uncertain prognostic value. These include molecular characteristics (11, 12, 20). Research on these molecules might not reveal their exact prognostic value, but can offer suggestions for therapeutic targets.

In general, the choice of an adjuvant therapy, used before clinical evidence of metastasis, is based upon regimens that show activity against proven systemic disease. So far, no such treatment has proven to be particularly effective. Therapies, which showed isolated patient responses, should thus first be evaluated in controlled studies.

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