Metastatic uveal melanoma: is there a role for conventional chemotherapy? – A single center study based on 58 patients

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Uveal melanoma metastases develop in 6.5–35% of patients, most commonly to the liver. Metastatic uveal melanoma (MUM) survival is poor, with 5–7 months of median survival. We reviewed retrospectively all patients with MUM diagnosed between January 1990 and December 2008 at our institution. We analyzed a total of 58 patients with a median age of 61 years (31–84 years). Median time for metastases development was 25.63 months (0.17–102.43 months). Fifty-six patients had hepatic involvement, 63.8% bilobar and 51.7% had more than or equal to five hepatic metastatic lesions. Sixteen patients (27.6%) had two or more organs involved. Six patients (10.71%) were treated with surgery, 25 patients (44.67%) received systemic chemotherapy, and 23 (41.07%) had best supportive care (BSC). The median overall survival (OS) for all the patients was 10.83 months [95% confidence interval (CI): 6.92–14.74]. Patients who had undergone chemotherapy presented 10.83 months (95% CI: 5.35–16.308) of median OS whereas the patients who did not undergo this treatment had an OS of 8.033 months (95% CI: 2.46–13.61). There were more patients with poor survival characteristics such as worse Eastern Cooperative Oncology Group performance status in the BSC group. OS was poor in treated and BSC patients. Differences in survival are more likely to be related to patient characteristics rather than to a chemotherapy effect. Patients with MUM should be included in clinical trials evaluating other options with newer agents. Melanoma Res 00:000–000 © 2011 Wolters Kluwer Health | Lippincott Williams & Wilkins.

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Introduction

Uveal melanoma is a rare disease accounting for 0.1% of all cancer deaths. This disease arises from melanocytes of the uveal tract and is the most common primary intraocular tumor in adults, with an incidence estimated at 0.6 per 100,000 persons/year in the Western population and seems to have remained stable over time [1]. Metastases from uveal melanoma appear in 6.5–35% of the patients during the first decade. The clinical and metastatic behavior differs from cutaneous melanoma because of its initially purely hematogenous dissemination and its tendency to metastasize to the liver. Furthermore, the liver is almost a ‘sentinel lymph node’ for uveal melanoma because it is involved in 95% of patients and can be the sole site of metastasis [2]. This specific oculo-hepatic tropism remains unexplained [3]. When liver metastases develop, the prognosis is poor and life expectancy reduces to less than 6 months in the absence of treatment [4]. Only a few prognostic factors for survival have been identified. Age, short time interval to metastases development, and importance of liver metastasis burden have been shown a negative impact on survival, whereas patients diagnosed at regular follow-up survive significantly longer, probably because of earlier diagnosis before symptoms appear [2,5]. Several loco-regional treatment options can be considered if metastases are confined to the liver, including partial hepatic resection or radiofrequency ablation [4]. Curative resection is possible in only a small fraction of patients because of the number, location, or size of the metastases [6]. Systemic chemotherapy is usually unsuccessful in metastatic uveal melanoma and results in an objective response rate that ranges from 5 to 15%. There is no proof that conventional chemotherapy prolongs survival which remains between 2 and 7 months with only 15% of patients alive at 1 year [7–9]. Most therapies are derived from the experience extrapolated from cutaneous melanoma. As there is no proof that chemotherapy ever prolongs survival in metastatic uveal melanoma patients, and as a phase 3 trial in metastatic uveal melanoma has...
never been performed, such a trial that answers how chemotherapy improves survival in this setting will never be conducted. Therefore, we hypothesize that the retrospective analysis of disease and data from a group of patients affected with metastatic uveal melanoma diagnosed at one single institution, following the same follow-up and treatment protocols for almost over 20 years, might allow us to analyze the role of chemotherapy in this clinical situation.

**Patients and methods**

**Study population**

Six hundred and eleven patients who were diagnosed with uveal melanoma between January 1990 and December 2008 were identified from the databases of the Hospital Universitari de Bellvitge and the Catalan Cancer Institute. Clinical records were reviewed to obtain patient demographics, primary tumor characteristics, and follow-up information. The primary tumor treatment was surgery, enucleation, or local resection for 219 patients while 390 patients were treated with brachytherapy following our institution protocols. Two patients received external beam radiotherapy because they refused enucleation and were not suitable for brachytherapy.

After completion of primary tumor treatment, all patients were visited periodically using the same follow-up protocol. Physical examinations including ophthalmological exploration, abdominal ecography, and lactate dehydrogenase (LDH) determination were performed every 6 months. In addition, a chest radiograph was taken every 12 months. Diagnosis of recurrence was made on the basis of imaging and, if necessary, cytological analysis or biopsy was carried out. An elevated LDH level as a solitary finding was not accepted as evidence of relapse. All liver relapses were discussed at the hepatic surgery committee at the Hospital Universitari de Bellvitge. This committee consisted of hepatic surgeons, radiologists, and medical oncologists who discuss all clinical reports available and try to select patients who could benefit from a local therapy because of the low metastatic tumor burden.

**Statistical analysis**

This study was based on an analysis of a consecutive and retrospective case series. The database was updated on December 2008; and sample size was based on the number of consecutive patients who met the study criteria between January 1990 and December 2008. Variables were collected retrospectively from the case report forms. All analyses were carried out using the Statistical Package for the Social Sciences for Windows, version 14 software (SPSS Inc., Chicago, Illinois, USA). Summary tables (absolutes and relative frequencies) were used for descriptive analysis of categorical variables. Central value, average or median, and their value ranks or 95% confidence intervals (CIs) were applied as continuous variables and were compared with a Student’s t-test analysis. The χ²-two-tailed test was used as appropriate for a comparative analysis between categorical variables in the patients treated with chemotherapy and best supportive care (BSC) protocols, and to determine which ones were better predictors of survival. A P value of less than 0.1 was considered statistically significant with the aim of identifying differences between both groups. The Kaplan–Meier product limit estimator was used to estimate the survival distribution. The univariate and multivariate analyses compared the patients treated with chemotherapy and BSC protocols using Cox proportional hazards model. A Wald forward selection procedure with a selection criterion of P value less than 0.05 was performed to identify the significant variables. The best model was constructed by considering the variables entered by this sequential method of Wald.

**Results**

**Characteristics of the patients and treatment**

A total of 58 patients (24 men and 34 women) developed systemic relapse during the follow-up period after a radical local therapy. The median age at disease relapse was 61 years (range: 31–84 years). Primary tumor site and primary tumor treatment are reported in Table 1. The overall median time between primary tumor treatment and diagnosis of metastatic disease was 25.63 months (range: 0.17–102.43 months), and at that time 38% of patients were asymptomatic, whereas 34% and 14% were minimally symptomatic and symptomatic, respectively. We consider patients to be minimally symptomatic when they presented mild symptoms due to metastatic disease that do not require medical intervention, and symptomatic when medical intervention is indicated due to metastatic disease.

Ninety-six percent of patients had hepatic involvement and only two did not have hepatic disease. Both of these patients presented isolated skin lesions that could be surgically removed. Only 16 patients presented extrahepatic synchronous metastases. All patients with relapse limited to the liver were discussed at the hepatic surgery committee, and only eight patients were considered to be suitable for local treatment, surgery, or radiofrequency ablation. More than 50% of patients presented with more than five hepatic metastases and bilateral involvement as seen in Table 1.

The remaining 48 patients with hepatic metastases received either chemotherapy or BSC, according to medical criteria, such as advanced age or medical conditions that contraindicate chemotherapy and patient preferences.
Twenty-five patients were treated with chemotherapy and will be included in the same group for the following analysis. Up to 13 patients received dacarbacine, five were treated with temozolamide with or without interferon, and the other five with fotemustine. The other schedules applied consisted of carboplatin/dacarbacine/interferon-\(\alpha\)/interleukin-2 treatment in the remaining two patients. Twenty-three patients were not considered for chemotherapy treatment because of medical conditions or refusal of treatment, and are included in the BSC group for the following analysis.

Clinical and disease characteristics differences between chemotherapy versus best supportive care group of patients

There were differences between patients treated with chemotherapy and those under BSC protocols as reflected in Table 2. The patients in the BSC group were older (\(P=0.022\)) than those of the chemotherapy group. Furthermore, the BSC group had a worse ECOG, so they were more symptomatic than the patients treated with chemotherapy. Nevertheless, there were no differences between the two groups with regard to other tumor features assessed such as LDH, number of hepatic metastases, location of metastases in the liver, extrahepatic metastases, and time to metastases diagnosis.

Survival analysis

Median duration of the follow-up was 8.87 months (range: 0.36–88.03 months). Patients who were suitable for local treatment such as hepatic surgery or radiofrequency ablation, were not assessable for overall survival because of the small number of patients and events. The median overall survival was 10.83 months (95% CI: 6.92–14.74) for all patients as represented in Fig. 1. Median overall survival in the chemotherapy group was 10.83 months (95% CI: 5.35–16.30), whereas it was 8.03 months (95% CI: 2.46–13.61) in the BSC group.

Univariate and multivariate analyses

The number of hepatic metastases was the only factor that was shown to be a predictor of survival in the univariate analysis with a hazard ratio (HR) of 3.059 (1.36–6.87) (Table 3). Survival was significantly influenced by the number of hepatic metastases (HR: 5.65, 2.2–14.5) and ECOG (HR: 2.4, 1.06–5.8) in the multivariate analysis (Table 3). Treatment with chemotherapy was neither significant in the univariate analysis nor in the multivariate analysis in our cohort of patients.
Discussion

Treatment of metastatic uveal melanoma has not been investigated systematically in randomized trials. To date, no randomized trial has been reported to show the superiority of any therapeutic strategy to BSC, as in its cutaneous counterpart. A variety of cytotoxic agents have been investigated, such as dacarbazine, treosulfan, temozolamide, fotemustine, cisplatin, and combination therapies like bleomycin + vincristine + lomustine + dacarbazine [7–10]. The response rates range from 0 to 15% in larger trials with a median survival of 6–12 months. Higher response rates and median survival have been reported with chemotherapy administration directly into the hepatic artery in a highly selected group of patients [6,11]. The question whether intra-arterial hepatic chemotherapy is better than infusion through peripheral vein will be answered by a large phase 3 trial opened by the melanoma group of the European Organization for Research and Treatment of Cancer (EORTC). The European Organization for Research and Treatment of Cancer protocol 18021 compares intra-arterial hepatic fotemustine administration with the same drug used intravenously. The primary end point of this trial is overall survival. In our experience, only 10% of relapsed patients could be selected for local hepatic treatments and up to 30% had extrahepatic metastatic disease, therefore there is a high proportion of patients who would be candidates for a systemic approach rather than a hepatic directed therapy administration.

There is no optimal chemotherapy for metastatic uveal melanoma but the treatment regimens used in this study have at least shown some activity in this disease and more active schedules are not available. Half of them received dacarbazine in monotherapy. It is still the most advocated treatment in combination or in monotherapy in melanoma, but uncertainty remains with regard to the level of activity in uveal melanoma as opposed to cutaneous melanoma. Bedikian et al. [12], on the basis of a retrospective review of cases treated at the MD Anderson Cancer Centre, concluded that standard systemic chemotherapy was inactive with a response rate as low as 1%. In contrast, Flaherty et al. [13] reported that both uveal and cutaneous melanomas have similar response rates on the basis of their experience with patients entered into seven consecutive phase 2 trials carried out by the South West Oncology Group. Temozolomide was used in five patients, four of them in a clinical trial in combination with interferon-α2b. Temozolomide in monotherapy has been shown not to be effective for this disease but the experience of combining this drug with interferon-α2b in uveal melanoma has never been reported [10]. Another two patients received different biochemotherapy schedules. Biochemotherapy has had limited evaluation for efficacy against metastatic uveal melanoma. In contrast to in-vitro data which suggests that interferon-α has an action on human melanoma cell lines [14], immunotherapy with interferon-α2b administered alone or with interleukin-2 has shown only few minor responses [15]. The experience with cutaneous melanoma has shown that biochemotherapy is superior to chemotherapy alone with regard to response rate and progression-free survival but with similar overall survival and higher toxicity [16]. However, the two phase 2 trials with better survival in uveal melanoma are the only ones that combine interferon-α with...
bleomicin + vincristine + lomustine + dacarbazine or fotemustine [8,9]. Another five patients were treated with fotemustine, a nitrosourea that is characterized by a high hepatic extraction rate. This drug, despite its poor results in a phase 2 trial [9], has one of the best response rates and overall survival data compared with other schedules, and it has been adopted as a standard for treatment in this group of patients by European groups.

These results are in line with published data and confirm that uveal melanoma relapse is more common in the liver and has poor prognosis. Differences in overall survival between patients treated with chemotherapy and BSC were small. This is not a clinical trial, so it is not statistically appropriate to compare both groups of patients directly. Above all, when we compare patients and disease characteristics among patients treated with chemotherapy or BSC, only differences in age and ECOG performance status were significant. We did not identify significant differences in LDH, number of hepatic metastasis, nor time to metastasis development between both the groups. Moreover, clinical characteristics such as age or performance status have been described as important prognostic factors for neoplastic diseases [17].

Several characteristics of the primary tumor have been identified as prognostic factors for metastatic relapse such as ciliary body involvement, extrascleral extension, diameter and location of the anterior margin of the tumor, cell type, cytornorphometric features, presence of mitotic figures, tumor-infiltrating lymphocytes and macrophages, the presence of vascular loop, and pigmentation [18,19]. In this cohort, all patients are metastatic and only few prognostic factors have been identified to date which refer to this clinical situation. There are only six studies that provide a multivariate analysis of these factors [2,5,12,20–22]. To summarize these studies, age, male sex, short interval of time between uveal melanoma primary treatment and metastasis diagnosis, and factors related with the severity of liver metastatic burden such as poor performance status, elevated percentage of hepatic replacement, large metastasis diameter, and abnormalities in liver function tests including LDH, have been shown to have a negative impact on survival. The limitation of most of these studies is that they refer to limited number of metastatic patients and may suffer from selection biases such as study population that are potential candidates for liver resection. Although, it is not the purpose of this study, the number of hepatic metastases was the only factor that was shown to be a predictor of survival in the univariate analysis. Survival was significantly influenced by the number of hepatic metastasis and ECOG performance status in the multivariate analysis. Patients in the BSC group had worse ECOG performance status and were more symptomatic than patients treated with systemic chemotherapy. Both groups of patients were well balanced for the number of hepatic metastases and other metastatic disease characteristics that could be related to bad prognosis. Treatment with chemotherapy was neither significant in the univariate analysis nor in the multivariate analysis in these patients.

In the presence of these results, it is concluded that survival differences identified in these cohort of patients are most likely to be related to the patients’ characteristics such as performance status, rather than any chemotherapeutic effect. There are several limitations in this study. First, the low number of patients that make a statistical analysis difficult as it happens in the majority of studies performed in this clinical situation. In contrast, it is a really pure cohort because all patients have been treated in the same institution with the same follow-up protocol. Second, this is not a randomized clinical trial but a phase 3 trial, wherein randomizing patients to chemotherapy or BSC will never be performed because of difficulty in recruiting patients because of the low incidence of disease. Furthermore, the best understanding of the biology of cancer disease has allowed us to identify pathways that are important in mechanisms of proliferation, survival, or dissemination [3,23]. Recently GNAQ gene oncogenic mutation has been identified in nearly 50% of primary uveal melanomas [24]. The emergence of newer agents that target this or other pathways make the concept of this large randomized trial less attractive. To summarize, patients with metastatic uveal melanoma should be included in clinical trials evaluating other options with newer agents with potentially less toxicity and greater efficacy than conventional chemotherapy.

References


