Imaging in Interventional Radiology
ISSN: 2471-8564

Open Access Review Article

Retrospective Analysis of Patients Treated with Minimally Invasive Therapies to Control Hepatic Metastases from Choroidal Melanoma

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ABSTRACT

Introduct on: Some rarer types of melanoma include uveal melanoma, which arises from the uveal tract in the eye. This type of neoplasm accounts for about 5% of melanoma cases. It is the most common intraocular tumor in adults and has a different clinical and evolutionary course from cases of cutaneous melanoma, with special involvement of the liver. About 50% of patients diagnosed with uveal melanoma develop isolated liver metastases with a median survival of 2 months-7 months.

Materials and methods: This work is a retrospective, unicentric cohort study. It was submitted and approved by the research ethics committee. The radiological response, adverse effects and complications of the treatment modalities performed were evaluated.

Results: 16 patients were treated with either hepatic embolization or intra-arterial chemotherapy. The mean age of patients was 65 years with diagnosis at 56 years. 10 patients were female and 6 were male. 15 patients had primary Choroidal melanoma and 1 patient had cutaneous melanoma. 68% of patients were initially treated with brachytherapy and 25% with enucleating.

Discussion: This study has several limitations in statistical terms, mainly considering the small number of cases analyzed. There were also difficulties in extracting all the necessary data in an ideal way due to the omission of some information in the medical records and also the lack of some control exams for different reasons.

Conclusion: Twenty-three cycles of fotemustine treatment were performed, divided into induction and maintenance phases. The group of patients treated with fotemustine had more extensive disease with a consequent higher number of toxic complications when compared to embolization. To measure the degree of complication related to the procedures, the guideline of the Cardiovascular and Interventional Radiological Society of Europe (CIRSE) was used.

Keywords: Uveal melanoma; Fotemustine treatment; Fotemustine; Radiological response; Adverse effects

Received:	17-November-2022	**Manuscript No:**	IPJIIR-22-14841
Editor assigned:	21-November-2022	**PreQC No:**	IPJIIR-22-14841 (PQ)
Reviewed:	05-December-2022	**QC No:**	IPJIIR-22-14841
Revised:	17-January-2023	**Manuscript No:**	IPJIIR-22-14841 (R)
Published:	24-January-2023	**DOI:**	10.21767/2471-8564.23.6.35

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Citation: Caires Gois FW (2023) Retrospective Analysis of Patients Treated with Minimally Invasive Therapies to Control Hepatic Metastases from Choroidal Melanoma. J Imaging Interv Radiol. 6:35.

INTRODUCTION

Some rarer types of melanoma include uveal melanoma, which arises from the uveal tract in the eye. This type of neoplasm accounts for about 5% of melanoma cases. It is the most common intraocular tumor in adults and has a different clinical and evolutionary course from cases of cutaneous melanoma, with special involvement of the liver. About 50% of patients diagnosed with uveal melanoma develop isolated liver metastases with a median survival of 2 months-7 months.

In recent years there has been a significant increase in the use of endovascular therapies including embolization, chemoembolization, radio embolization, hyperthermia chemotherapy, immunoembolization and intra-arterial infusion of chemotherapy for the treatment of liver metastases. Therapies with intra-arterial infusion have high antitumor activity due to the high concentrations of chemotherapy in the infused territory, which can reach up to 20 times-40 times the serum levels in relation to the intravenous route. Local treatment also exposes the patient to fewer chemotherapy related systemic effects.

The high concentration of chemotherapy achieved is capable of maintaining an antineoplastic effect even with already refractory lesions, due to the expressive increase in the concentration above the threshold tolerated by the tumor. Another important factor is the predominantly arterial irrigation of metastatic liver tumors.

Studies with endovascular treatments such as embolization for the treatment of melanoma metastases bring very heterogeneous results due to the lack of standardization of methods. Increased survival ranges from 5 months to 29 months with regimens that include embolization and chemoembolization. For more than 20 years, several therapeutic regimens of embolization, chemoembolization and intra-arterial chemotherapy have been used in the treatment of uveal melanoma, but to date there are no well-established protocols in the literature or prospective studies comparing the various chemoembolization/chemotherapeutic regimens.

The best results were demonstrated from the use of intra-arterial chemotherapy with fotemustine. Fotemustine is a chemotherapeutic drug from the nitrosourea group that exerts an antineoplastic effect by interfering with the functioning of the guanine and cytosine bases, preventing DNA synthesis with consequent apoptosis. When administered intravenously, it has a high hepatic extraction 8 times-47 times the serum values. It was introduced in the intra-arterial treatment of liver metastases based on previous regimens used in the treatment of cutaneous melanoma. Of the various studies performed with fotemustine, there was an increase in survival ranging from 10 months-24 months. Some authors have not reported a significant benefit in relation to intra-arterial use in terms of overall survival, but with an increase in progression free survival.

The treatment regimen proposed by Leyvraz is used in this work. This regimen constitutes an initial attack phase with intra-arterial infusion of fotemustine at a dose of 100 mg/m^2 on days 1, 8, 15 and 22, followed by a 5 week break. The maintenance phase is then started with an infusion of 100 mg/m^2 every 3 weeks.

For chemotherapy infusion, catheterization of the hepatic artery that nourishes most of the tumor is performed, following standard precepts of endovascular arterial approach. Then, fotemustine is administered in an infusion pump for 1 hour.

Patients are followed for the most common adverse effects related to chemotherapy, such as thrombocytopenia, neutropenia and liver toxicity. The degree of adverse effects dictates the suspension or maintenance of treatment.

This study aims to evaluate the radiological response rate, complications and adverse events related to interventional endovascular treatment as palliative therapy for patients with hepatic metastasis of choroidal melanoma [1-8].

LITERATURE REVIEW

This work is a retrospective, unicentric cohort study. It was submitted and approved by the research ethics committee. The radiological response, adverse effects and complications of the treatment modalities performed were evaluated.

The study population consisted of all patients undergoing loco regional treatment with embolization, or intra-arterial chemotherapy for the treatment of hepatic melanoma metastasis with predominant or exclusive liver metastases and patients that have performed any of the treatments: Embolization and/or intra-arterial chemotherapy.

Patients were selected from 2014 to the present date. All patients were followed up periodically with imaging and laboratory controls monthly after each treatment cycle. The response rate followed the RECIST 1.1 (Response Evaluation Criteria in Solid Tumors) standards. There were no losses to follow-up of the patients. The data obtained were stored in a database for statistical analysis using SPSS version 20.0.

Study variables were sex, age at diagnosis, type of treatment at the primary site, type of treatment performed (embolization or intra-arterial chemotherapy), type of embolic material, volume of embolic material, volume of liver disease measured by RECIST 1.1 criteria before and after treatment, time to progression, progression free survival and objective response rate.

For statistical analysis, Student's t test (or non-parametric Mann-Whitney test, as indicated) will be used to compare quantitative variables between two groups. For the study of qualitative variables, 2 × 2 and 2 × 3 tables will be used, with evaluation of statistical significance by pearson's *chi-square* test with Yates' correction or Fisher's exact test, when indicated. To assess the association between two

continuous variables, the Pearson (r) or Spearman (rho) correlation coefficient will be used, as indicated. Results with a type I error probability lower than or equal to 5% ($p \leq 0.05$) will be considered statistically significant.

For multivariate analysis, binary logistic regression will be performed, using the radiological response as the dependent variable. The Odds Ratio (OR) of all variables will be calculated and results with $p<0.05$ will be considered statistically significant.

For analysis of progression-free time, the Kaplan-Meyer curve will be used. To compare the progression free time curve in different groups, the log rank test and cox regression will be used. The significance level adopted will be 5% [9-15].

RESULTS

16 patients were treated with either hepatic embolization or intra-arterial chemotherapy. The mean age of patients was 65 years with diagnosis at 56 years. 10 patients were female and 6 were male. 15 patients had primary choroidal melanoma and 1 patient had cutaneous melanoma. 68% of patients were initially treated with brachytherapy and 25% with enucleation. There were 5 deaths during the follow-up period, 2 from liver failure, 1 from sepsis, 1 from hepatorenal syndrome and 1 from multiple organ failure. The mean age of death was 62 years, with a mean duration of approximately 7 years or 84 months from diagnosis to death, ranging from 3 years to 13 years. Survival from the start of loco regional treatment to death was 15.4 months. There was 1 in-hospital death 16 days after the procedure, due to renal and hepatic complications unrelated to the procedure. This case was excluded from the analysis.

A total of 53 cycles of treatment with chemotherapy (fotemustine) or embolization (with several different agents) were performed. 23 cycles of fotemustine treatment and 30 cycles of embolization of liver lesions were performed using various micro particles.

All cycles were evaluated for complications using the CIRSE scale. Complications greater than or equal to level 2 were marked for comparison; the remainder was omitted from the analysis. A total of 18 cycles with grade 2 or more complications were recorded. There was no difference in terms of complications by CIRSE between treatments with embolization and chemotherapy.

In the fotemustine group we had 2 cases of drug hepatitis, which were treated conservatively without sequelae. One of the patients needed to stay in the hospital for longer due to the very significant increase in bilirubin after the procedure (>15 mg/dL), but she obtained spontaneous improvement with conservative treatment.

We also had 1 case of death in the fotemustine group during the same hospitalization, 16 days after the treatment cycle for renal and hepatic failure.

In absolute terms, we had more grade 3 and 4 complications in the fotemustine group, but without statistically significant differences [16-20].

Regarding the RECIST 1.1 response criteria, 3 patients achieved a partial response, 8 remained with stable disease and 2 progressed despite treatments. Which predicts a 23% response rate? Most of our patients met criteria for stable disease; 62% of treated cases remained stable for most of the treatment, with good quality of life. If we add the cases of partial response with stable disease, we obtain 85% of cases free of progression during treatment. The remaining 15% of patients progressed despite treatment. We had 3 cases that did not allow an ideal evaluation during all cycles, for better data quality these cases were omitted from the sample for calculation. In the fotemustine group we had 2 cases of progression while in the embolization group most patients remained with stable disease. Some patients in the embolization group progressed later with confirmed extra hepatic progression, which led to the termination of loco regional treatment.

A comparison of the reduction in centimeters of lesions between the different types of treatment was also performed. There was a more expressive reduction in the size of the lesions in the embolization group, while the fotemustine group showed a slow growth (still configuring a stable disease <30%). In general, it was noted that the fotemustine group achieved a smaller global reduction in lesion diameters, although this had no impact on radiological response according to RECIST 1.1 criteria.

In temporal analysis, the mean time to progression was 16.6 months, 16.2 months for the embolization group and 15.2 months for the fotemustine group. There was no statistical difference regarding the time of progression and the type of treatment performed with embolization or intra-arterial chemotherapy with fotemustine. 1 patient was excluded from the analysis because he had performed the two treatments sequentially, first embolization and then fotemustine. There were no statistically significant differences in the analysis of relative risk and odds ratios that favored any of the treatment groups. The long rank test also showed no statistically significant difference in the distribution of events in the two groups.

DISCUSSION

This study has several limitations in statistical terms, mainly considering the small number of cases analyzed. There were also difficulties in extracting all the necessary data in an ideal way due to the omission of some information in the medical records and also the lack of some control exams for different reasons. This work was not designed for the analysis of overall survival, being statistically flawed in the detection of this outcome.

General Data

The most common initial treatment was brachytherapy with some cases of enucleation at a second stage. 68% of patients

were successfully treated with brachytherapy and 25% with enucleation. On average, a latency period of 7 years was observed until the onset of metastatic liver lesions, with subsequent initiation of loco regional treatment with embolization and/or chemotherapy.

The rationale of loco regional treatment aimed at the liver is to preserve liver function as much as possible by preventing/delaying the progression of metastases, which in the final stage of the disease infiltrate most of the parenchyma leading to irreversible liver failure and death.

Before starting treatment, patients were evaluated for the volume of liver disease. Patients with more localized and well-defined lesions are submitted to embolization with microparticles.

Patients with greater disease volume, with miliary pattern lesions or advanced bilateral disease, were submitted to the intra-arterial chemotherapy regimen with fotemustine following the protocol with attack and maintenance phase described by Leyvraz.

Treatment with fotemustine showed results consistent with those described in the literature. The median survival after starting locoregional treatment was 15.4 months, close to those described by Leyvraz of 12 months and peters of 15 months. Leyvraz also conducted another study in 2014 with 171 cases of intra-arterial chemotherapy with fotemustine, achieving a median survival of 15 months. Most studies show a median survival of 12 months-24 months.

The group treated with fotemustine had a case of very early death after completion of the treatment cycle, with the patient dying 16 days after the procedure. The reason for death was derived from the development of hepatorenal syndrome, with progressive dysfunction of renal function and death from renal and hepatic failure. This patient was removed from the survival analysis.

Complications

Twenty three cycles of fotemustine treatment were performed, divided into induction and maintenance phases.

The group of patients treated with fotemustine had more extensive disease with a consequent higher number of toxic complications when compared to embolization.

To measure the degree of complication related to the procedures, the guideline of the Cardiovascular and Interventional Radiological Society of Europe (CIRSE) was used. This guideline was created with the aim of standardizing the description of complications related to interventional procedures, dividing complications into progressively more complex degrees ranging from 1 to 6.

In general, grade 2 and above events are predictors of greater severity and reflect a more toxic effect of treatment.

A total of 18 treatment cycles with complications of grade 2 or more were observed. In the fotemustine group, we had 2 cases of secondary hepatitis presumably related to chemotherapy, with 1 of the cases requiring hospitalization for more than 2 weeks, both treated conservatively and without major sequelae. The fotemustine group had a higher mean score for complications in absolute terms, but there was no statistical difference in relation to the group treated with embolization.

One explanation for this phenomenon comes from the usual indication of treatment involving more severe patients. Patients who are selected for treatment with fotemustine naturally have a greater volume of liver involvement by metastases, more disseminated lesions and diffuse infiltration of the parenchyma. These characteristics advocate a lower tolerance profile, with less healthy liver parenchyma and a greater propensity to decompensate liver function. Another explanation may also be related to the intrinsic toxicity profile of the chemotherapy drug, which is exposed in high serum concentrations in the liver after intra-arterial infusion.

It is also possible that the statistical difference was not relevant due to the small number of patients analyzed. Perhaps a larger group of cases would be able to really delineate differences in terms of toxicity.

In the group of patients treated with embolization, 30 cycles of treatment with micro particles of different types and sizes were performed. This group of patients had, in most cases, more localized disease with the possibility of super selective targeted therapy.

The profile of complications in this group of patients was more related to postoperative pain as part of the post-embolization syndrome. Patients with melanoma metastases have healthy liver parenchyma, which is sensitive to the embolic effect and generates post-surgical pain in most patients. Cases of patients with CIRSE grade 2 or 3 complications arise from prolonged hospital stay for pain management. There were no cases of liver dysfunction, non-target organ embolization or vascular injury from dissection or perforation.

Radiological Response

Regarding the criteria for radiological response after treatment, the criteria of RECIST 1.1 (Response Evaluation Criteria in Solid Tumors) were used. Of the 16 initial patients, 3 cases had to be excluded due to inadequacy in relation to the sequence of control exams necessary for follow-up.

Of the remaining patients, 3 patients had a partial response, characterized by a reduction in the size of the lesions greater than 30%. 8 patients remained with stable disease, which is not suitable for progression or partial response. And we had 2 cases that showed lesion growth >20% or emergence of new nodules. In absolute terms, the radiological response rate was 23% and the stable disease rate was 62%.

The loco regional liver disease control rate was estimated to be 85% for both treatments (fotemustine + embolization).

The fotemustine group achieved a radiological response rate of 50%.

The embolization group did not experience any case of liver progression during the treatment follow-up period with a control rate of 100%. Treatment with embolization was discontinued due to extrahepatic progression.

We achieved loco regional control rate with fotemustine very close to that described in the main references, with data ranging from 13% to 40%.

Despite the higher radiological response rate observed in this study, there were no differences in terms of survival time and progression free survival.

The embolization group showed no statistically significant differences in terms of overall survival and progression free survival despite greater loco regional control of liver disease.

A comparison of the variation in lesion size in centimeters was performed in relation to the agents used for treatment, including fotemustine and various micro particles as embolic agents.

A test with analysis of variance was performed considering the type of agent used and the value of the reduction in lesion sizes. There were no statistically significant differences between the different groups of embolic agents and fotemustine when considering the degree of lesion reduction.

In absolute terms, the fotemustine group showed growth of about 0.5 cm in RECIST 1.1 at each treatment cycle.

The embolization group showed a reduction with all the subtypes of micro particles used. The greatest absolute reductions were obtained with calibrated micro particles of 100 microns, with an average reduction of 2.9 cm per treatment cycle in the sum of the RECIST 1.1 diameters. The most used micro particles were particles of 100 microns-300 microns, with an average reduction of 0.3 cm of lesions in each treatment cycle.

Once again, we observed a more positive and expressive effect of the embolization group in relation to the group of patients treated with intra-arterial chemotherapy with fotemustine, but these results are greatly influenced by the treatment indication itself.

Patients undergoing embolization have more limited local disease, which improves results in terms of absolute reduction in lesion diameters. This favors more robust results in terms of radiological response in the embolization group, but without long-term differences in terms of survival.

Progression

In the literature, progression-free survival with fotemustine ranges from 4.5 to up to 24 months. In our analysis, survival from diagnosis was 16.6 months considering both groups and 16.2 months for the embolization group *vs*. 15.2 months for the fotemustine group.

There were no statistically significant differences in the analysis of survival with the long rank test between the two groups, reaching p of 0.71.

Although there were no statistical differences between the two groups, it is interesting to note that even with a profile of patients with more advanced and bulky disease, the group treated with fotemustine behaved similarly in terms of progression when compared to the group with more restricted disease.

CONCLUSION

These findings strongly favor treatment with intra-arterial chemotherapy even in an initially unfavorable context, such as when there is a large number of liver metastases. Even with increased risk of hepatotoxicity and loss of organ function.

The risk analysis and odds ratio for considering the risk of progression was 0.44 for the fotemustine group *vs.* 1.55 for the embolization group, with p of 0.22 and 0.47 respectively, both without statistical significance. Here, we observed a trend towards a higher risk of progression in the group treated with embolization, probably due to the higher absolute number of patients treated with embolization. As the sample of patients treated with fotemustine was proportionately smaller, these differences are believed to have biased the analysis. The sample also has a small n that may fail to detect relevant differences in these two groups.

A multivariate analysis was also performed considering the progression outcome using the variables of type of treatment, material used, volume of embolic agent used, lesion size by RECIST 1.1 and complications.

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