Pergamon

European Journal of Cancer, Vol. 34, Suppl. 2, pp. S27–S30, 1998

Printed in Great Britain
0959-8049/98 $19.00+0.00

PII: S0959-8049(97)10161-7

Original Paper

The Treatment of Metastatic Uveal Melanoma

S. Pyrhönen

Department of Oncology and Radiotherapy, Turku University Central Hospital, PO Box 52, 20521 Turku, Finland

Malignant melanoma can occur in various ocular structures and accounts for 70% of all primary eye malignancies. At the time of initial diagnosis of uveal melanoma, most patients have no demonstrable evidence of metastatic disease. However, within 5 years, metastases appear in 19–35% of patients. The median relapse-free interval for these patients is 2–4 years. Unlike cutaneous melanoma, uveal melanoma most commonly metastasises to the liver. In fact, the liver is the sole site or the initial site of metastasis in more than 50% of patients. This paper reviews major studies that evaluated different treatment options for metastatic uveal melanoma, including surgery, systemic chemotherapy, intra-arterial chemotherapy, chemoembolisation and chemoimmunotherapy. Surgery and systemic chemotherapy offer minimal benefits for these patients. However, the use of intra-arterial fotemustine demonstrated a 40% response rate for patients with liver metastases of uveal melanoma. Additionally, chemoimmunotherapy with a four-drug chemotherapy regimen and interferon alfa has provided response rates of approximately 20% and may contribute to prolonged survival. Ongoing multicentre trials are expected to determine the feasibility of this regimen. The activity of immunotherapy, particularly interferon, encourages its use in combination with other active therapies, such as intra-arterial fotemustine. © **1998 Published by Elsevier Science Ltd. All rights reserved.**

Key words: melanoma, uveal melanoma, eye neoplasm, neoplastic metastases, treatment
Eur J Cancer, Vol. 34, Suppl. 2, pp. S27–S30, 1998

INTRODUCTION

MALIGNANT MELANOMA, the most common primary intraocular malignancy, accounts for 70% of all primary eye malignancies. The annual age-adjusted incidence is reported to be 5–7 cases per million population in most countries. It occurs in all age groups, but nearly two thirds of cases are identified in the fifth to seventh decades. The natural history of uveal melanoma is poorly understood, partly because the primary tumour usually is not diagnosed until it is large enough to cause visual disturbance or other ocular symptoms.

During the last 20 years, primary uveal melanoma treatments that allow preservation of the eye and some remaining eyesight (i.e. plaque brachytherapy, charged particles and local resection) have progressed greatly; however, these treatments have not affected the rate of metastases as compared to enucleation [1–3]. Metastases appear in 19–35% of patients within 5 years [4–7] and the median relapse-free interval for these patients is 2–4 years [6–11]. Uveal melanoma most commonly metastasises to the liver, followed by lungs, bone and skin [7–10, 12]. The liver is the sole site or the initial site of metastasis in more than 50% of patients [11]. Uveal melanoma also has an unusual propensity for late hepatic metastases [8]. This pattern of dissemination differs from that of cutaneous melanoma, which preferentially metastasises to the lymph nodes, lung and brain rather than to the liver [8, 12–14].

Treatment options for metastatic uveal melanoma include surgery, systemic chemotherapy, chemoembolisation, intra-arterial chemotherapy and chemoimmunotherapy. Because metastatic uveal melanoma is rare, many of the literature reports contain few patients or are case reports, with only a few series containing more than 10 patients treated with the same protocol. This paper will review the major studies on the treatment of this disease and suggest perspectives for future studies.

Prognostic factors for metastatic uveal melanoma

Knowledge of the natural disease history after detection of metastases is necessary to understand current treatment options. Metastatic uveal melanoma has a poor prognosis; more than half of patients die within 5 months [1, 7, 12, 15]. Even with therapy, survival ranges from 1 to 59 months, with a median of 5–8 months [7–11, 16]. Various studies have defined prognostic factors for patients with metastatic uveal

melanoma. Young age, good performance status and female gender are associated with favourable prognosis, while the presence of liver involvement is an unfavourable prognostic factor [7, 10, 17]. A series of 201 patients with uveal melanoma who were treated at M.D. Anderson Cancer Center (Houston, Texas, U.S.A.) between 1968 and 1991 were analysed for tumour- and patient-related prognostic factors after diagnosis of liver metastases [16]. The authors used univariate analysis and then the multivariate stepwise regression method to determine the most important independent factors predicting survival. Among nine categorised parameters evaluated in the univariate analysis response to therapy, serum concentrations of alkaline phosphatase, lactate dehydrogenase and total bilirubin were significant factors influencing survival after the diagnosis of liver metastases. Patients' age and sex, the metastasis-free interval, presence of extrahepatic metastases and type of therapy for liver recurrence were not significant prognostic factors. However, in the multivariate stepwise regression analysis only the metastasis-free interval and serum alkaline phosphatase concentration significantly and independently influenced survival; total bilirubin concentration was of borderline significance.

TREATMENT OPTIONS

Surgery

Surgery combined with chemotherapy may be feasible in selected patients with one or few localised lesions. A remarkably long median survival of 18.4 months was observed after surgery and chemotherapy in 15 patients by Rajpal and coworkers [10]. Unfortunately, for the majority of patients, disease dissemination to the liver or other sites precludes this type of treatment.

Chemotherapy

Approximately 50 chemotherapeutic agents are presently available for the treatment of various malignancies. Most of these have been explored as systemic treatment for metastatic cutaneous melanoma and many have demonstrated activity against this disease, with 10–20% of tumours responding to treatment with single agents or drug combinations. Particularly, dacarbazine (DTIC) is a mainstay of treatment for metastatic cutaneous melanoma. In contrast, however, uveal melanoma lesions appear to be highly resistant to most available chemotherapeutic agents (Table 1).

The promising use of systemic chemotherapy for metastatic uveal melanoma was reported in the early 1970s [8]. 4 of 25 (16%; 95% confidence interval (CI), 5–36%) patients treated with DTIC and BCNU (carmustine) had a partial response. The Southwest Oncology Group (SWOG) also reported six responses (9%), including one complete and five partial responses, among 64 patients treated with either DTIC or cisplatin [17]. Other studies, however, using intravenous (i.v.) chemotherapeutic agents have provided minimal to no response. Experiences with various chemotherapeutic drugs over two decades at the M.D. Anderson Cancer Center detected only one partial response among 143 patients (95% CI, 0–4%) [16]. Similarly, the Eastern Cooperative Oncology Group (ECOG) did not demonstrate any objective responses in 51 patients with metastatic uveal melanomas who received various chemotherapeutic regimens [19]. The median survival in these two large groups of patients was 4.5 and 5 months, respectively. No objective responses were reported either among 24 patients treated in a German study with various chemotherapy protocols [11].

Chemoembolisation

Drugs with short half-lives that are rapidly cleared from the bloodstream have a pharmacokinetic advantage when given by regional infusion. Primary and secondary hepatic tumours obtain most of their blood supply from the hepatic artery, while normal hepatocytes are supplied primarily with blood from the portal circulation. Thus, chemotherapeutic agents have been administered through the hepatic artery. To enhance the efficacy of this type of treatment, embolising agents have been used prior to administering chemotherapeutic drugs to capture the drug locally and to slow its elimination from the tumour site.

Cisplatin alone or in combination with other cytotoxic agents has been administered in combination with embolisation agents like lipiodol through the arterial catheter directly into the liver and tumour arteries to achieve high and prolonged local drug concentrations (Table 2). Early reports of this treatment were promising. A response rate of 46% and a median survival of 11 months were reported by investigators at the M.D. Anderson Cancer Center [20]. Subsequently, however, the response rate dropped to 33% and the median survival of all treated patients was only 6 months [16]. Total failure of a similar treatment was recently reported by another institution [21].

Intra-arterial chemotherapy

Hepatic intra-arterial chemotherapy without embolisation has been explored using different types of drugs (Table 3). The majority of reports have been discouraging [16, 22], except for one recent report by a French and Swiss collaborative study group [23]. The investigators administered fotemustine, a new nitrosourea compound, directly into the hepatic artery of 30 patients with liver metastases from uveal melanoma. The dosage regimen consisted of 100 mg/m^2 given over 4 hours each week for 4 weeks, followed by a rest period of 5 weeks, after which fotemustine was administered every 3 weeks until progression. Four complete and eight

Table 1. *Response of metastatic uveal melanoma patients to systemic chemotherapy*

Therapy	*n*	Response CR/PR (%)	Median survival (months)	Reference
DTIC/BCNU	25	0/4 (16)	6	Einhorn and associates 1974 [8]
DTIC or cisplatin	64	1/5 (9)	5.0	Katato and associates 1995 [17]
DTIC/cisplatin/BCNU/TAM	16	0/1 (6)	ND	Nathan and associates 1994 [18]
Various	22	0/1 (5)	4.5	Rajpal and associates 1983 [10]
Various	24	0/0 (0)	9	Kath and associates 1993 [11]
Various	143	0/1 (1)	5	Bedikian and associates 1995 [16]
Various	51	0/1 (1)	4.5	Albert and associates 1996 [19]

ND, not defined; DTIC, dacarbazine; BCNU, carmustine; TAM, tamoxifen.

Table 2. Response of metastatic uveal melanoma patients to chemoembolisation

Therapy	*n*	Response CR/PR (%)	Median survival (months)	Reference
Cisplatin	30	1/13 (46)	11	Mavligit and associates 1988 [20]
Cisplatin-based (first-line)	44	1/15 (36)	6	Bedikian and associates 1995 [16]
Cisplatin-based (second-line)	20	0/5 (25)	ND	Bedikian and associates 1995 [16]
Cisplatin	14	0/0 (0)	6.6	Sato and associates 1995 [21]

ND, not defined.

Table 3. Response of metastatic uveal melanoma patients to intra-arterial therapy

Therapy	*n*	Response CR/PR (%)	Median survival (months)	Reference
Carboplatin	8	0/3 (38)	15	Cantore and associates 1994 [22]
Various (first-line)	24	0/2 (8)	ND	Bedikian and associates 1995 [16]
Various (second-line)	14	0/0 (0)	ND	Bedikian and associates 1995 [16]
Fotemustine	31	4/8 (40)	13	Leyvraz and associates 1996 [23]

ND, not defined.

partial responses were documented among 31 treated patients (40%; 95% CI, 22–59%). The median survival of treated patients also was remarkably long at 13 months. 3 patients (10%) were alive for more than 20 months. Disease progression was usually observed first in extrahepatic sites. These promising results warrant further research.

Chemoimmunotherapy

Development of biological response modifiers, such as interferons (IFN) and interleukin-2 (IL-2), for exogenous administration has provided a new modality of treatment for certain human malignancies. These drugs have demonstrated activity in the treatment of cutaneous melanoma [24, 25]. Table 4 provides results of studies using chemoimmunotherapy for metastatic uveal melanoma. Combining a four-drug chemotherapy regimen (DTIC, vincristine, bleomycin and lomustine; BOLD) with natural leucocyte interferon alpha (Finnferon-alpha), a response rate of approximately 60% in patients with disseminated nonocular melanoma was demonstrated [26]. Since a partial response also was observed in 2 of 4 patients with metastatic uveal melanoma, an extended phase II study was performed. 20 patients were included in the study, with the following metastatic sites: liver ($n = 16$), subcutis ($n = 3$), lung ($n = 3$), lymph nodes ($n = 2$), and orbita ($n = 2$). 19 out of 20 patients were assessable for response. Although there were no complete responses, 4 patients (20%; 95% CI, 6–44%) achieved a partial response. In addition, 10 patients (50%; 95% CI, 27–73%) experienced disease stabilisation for longer than 2 months. The median overall survival was 11.8 months, 4 patients survived over 2 years and 2 patients are still alive at 19 and 22 months. To confirm these favourable results, an extended multicentre European study (European Organization for Research and Treatment of Cancer (EORTC) protocol 88941) has been initiated that will replace leucocyte interferon with recombinant interferon alfa-2b in the treatment regimen. Also, investigators at Thomas Jefferson University (Philadelphia, Pennsylvania, U.S.A.) recently reported similar results using the same four-drug chemotherapy regimen (BOLD) with recombinant interferon alfa-2b [27]. Among 16 treated patients, three partial responses (19%; 95% CI 4–46%) and one minor response were observed. Survival in the partial responders has ranged from 9 months to greater than 2 years.

Additionally, two small studies have explored the use of IL-2 alone or in combination with DTIC or interferon alfa for metastatic uveal melanoma [28, 29]. In each study of 7 patients, no responses were documented.

CONCLUSIONS

Currently, metastatic uveal melanoma is an incurable disease that usually is treated palliatively. The use of various systemic chemotherapy regimens has been primarily unsuccessful and, thus, cannot be recommended for these patients. Hepatic intra-arterial chemotherapy combined with embolising agents is an interesting approach theoretically. Although early reports were very promising, subsequent studies have not confirmed the first enthusiastic results. However, this method requires further exploration, particularly with the use of other cytotoxic agents in addition to cisplatin.

Chemoimmunotherapy consisting of a four-drug chemotherapy regimen and interferon alfa demonstrates moderate activity in metastatic uveal melanoma and may contribute to prolonged survival. An ongoing multicentre European study of the BOLD regimen in combination with recombinant

Table 4. Response of metastatic uveal melanoma patients to chemoimmunotherapy

Therapy	*n*	Response CR/PR (%)	Median survival (months)	Reference
BOLD/IFN	16	0/3 (19)	ND	Nathan and associates 1995 [27]
BOLD/IFN	20	0/4 (20)	11.8	Pyrhönen and associates (Helsinki University Central Hospital, Helsinki)
IL-2 ± DTIC	7	0/0 (0)	4	Dorval and associates 1992 [28]
DTIC/IL-2/IFN ± TAM	7	0/0 (0)	ND	Atzpodin and associates 1995 [29]

ND, not defined; IFN, interferon; BOLD, bleomycin, vincristine, lomustine, DTIC; DTIC, dacarbazine; IL-2, interleukin-2; TAM, tamoxifen.

interferon alfa-2b will further elucidate the efficacy and tolerability of this regimen. Because intra-arterial fotemustine also has shown promise in patients with hepatic lesions, interferon-containing treatment combined sequentially with intra-arterial fotemustine in a rational fashion might be the next developmental step. Due to the rarity of this disease, multicentre collaborative research is of paramount importance.

1. Shields JA, Shields CL, Donoso LA. Management of posterior uveal melanoma. *Surv Ophthalmol* 1991, **36**, 161–195.
2. Adams KS, Abrahamson DH, Elsworth RM, *et al.* Cobalt plaque versus enucleation for uveal melanoma. Comparison of survival rates. *Br J Ophthalmol* 1988, **72**, 494–497.
3. Guthoff R, Frischmuth J, Jensen OA, Bjerrum K, Prause JU. Das aderhautmelanom: eine retrospektive randomisierte vergleichsstudie ruthnium-bestrahlung vs enukleation. *Klin Monatsbl Augenheilkd* 1992, **200**, 257–261.
4. Raivio I. Uveal melanoma in Finland; an epidemiological, clinical, histological and prognostic study. *Acta Ophthalmol* 1977, **133**(Suppl), 4–64.
5. Packard RBS. Pattern of mortality in choroidal malignant melanoma. *Br J Ophthalmol* 1980, **64**, 565–575.
6. Seddon JM, Albert DM, Lavin PT, Robinson N. A prognostic factor study of disease-free interval and survival following enucleation for uveal melanoma. *Arch Ophthalmol* 1983, **101**, 1894–1895.
7. Gragoudas ES, Egan KM, Seddon JM, *et al.* Survival of patients with metastases from uveal melanoma. *Ophthalmology* 1991, **98**, 383–389.
8. Einhorn LH, Burgess MA, Gottlieb JA. Metastatic patterns of choroidal melanoma. *Cancer* 1974, **34**, 1001–1004.
9. Bedikian AY, Kantarjian H, Young SE, Bodey GP. Prognosis in metastatic choroidal melanoma. *South Med J* 1981, **74**, 574–577.
10. Rajpal S, Moore R, Karakousis CP. Survival in metastatic ocular melanoma. *Cancer* 1983, **52**, 334–336.
11. Kath R, Hayungs J, Bornfeld N, Sauerwein W, Höffken K, Seeber S. Prognosis and treatment of disseminated uveal melanoma. *Cancer* 1993, **72**, 2219–2223.
12. Albert DM, Ryan LM, Borden EC. Metastatic ocular and cutaneous melanoma: a comparison of patient characteristics and prognosis. *Arch Ophthalmol* 1996, **114**, 107–108.
13. Zimmerman LE. Metastatic disease from uveal melanomas. The Bowman lecture: a review of current concepts with comments concerning future research and prevention. *Trans Ophthalmol Soc U.K.* 1980, **100**, 34–54.
14. Patel JK, Didolkar MS, Pickren JW, Moore RH. Metastatic pattern of malignant melanoma. A study of 216 autopsy cases. *Am J Surg* 1978, **135**, 807–810.
15. Albert DM, Niffenegger AS, Willson JKV. Treatment of metastatic uveal melanoma: review and recommendations. *Surv Ophthalmol* 1992, **36**, 429–438.
16. Bedikian AY, Legha SS, Mavligit G, *et al.* Treatment of uveal melanoma metastatic to the liver: a review of the M.D. Anderson Cancer Center experience and prognostic factors. *Cancer* 1995, **76**, 1665–1670.
17. Katato K, Liu PY, Sondak V, Flaherty LE. Survival and response to treatment in patients (PTS) with metastatic melanoma from intraocular primaries (MMIP) on SWOG studies (abstract). *Proc Am Soc Clin Oncol* 1995, **14**, 410.
18. Nathan FE, Sato T, Hart E, Berd D, Mastrangelo MJ. Response to combination chemotherapy of liver metastases from choroidal melanoma compared with cutaneous melanoma (abstract). *Proc Am Soc Clin Oncol* 1994, **13**, 394.
19. Albert DM, Ryan LM, Borden EC. Metastatic ocular and cutaneous melanoma: a comparison of patient characteristics and prognosis. *Arch Ophthalmol* 1996, **114**, 107–108.
20. Mavligit GM, Charnsangavej C, Carrasco CH, Patt YZ, Benjamin RS, Wallace S. Regression of ocular melanoma metastatic to the liver after hepatic arterial chemoembolization with cisplatin and polyvinyl sponge. *JAMA* 1988, **260**, 974–976.
21. Sato T, Nathan FE, Berd D, Sullivan K, Mastrangelo MJ. Lack of effect from chemoembolisation for liver metastasis from uveal melanoma (abstract). *Proc Am Soc Clin Oncol* 1995, **14**, 415.
22. Cantore M, Fiorentini G, Aitimi E. Intra-arterial hepatic caboplatin-based chemotherapy for ocular melanoma metastatic to the liver. Report of a phase II study. *Tumori* 1994, **80**, 37–39.
23. Leyvraz S, Spataro V, Bauer J, *et al.* Treatment of ocular melanoma metastatic to the liver by hepatic arterial chemotherapy. *J Clin Oncol* 1997, **15**, 2589–2595.
24. Kirkwood JM, Strawderman MH, Ernstoff MS, Smith TJ, Borden EC, Blum RH. Interferon alfa-2b adjuvant therapy of high-risk resected cutaneous melanoma: the Eastern Cooperative Oncology Group trial EST 1684. *J Clin Oncol* 1996, **14**, 7–17.
25. Rosenberg SA, Yang JC, Topalian SL, *et al.* Treatment of 283 consecutive patients with metastatic melanoma or renal cell cancer using high-dose bolus interleukin-2. *JAMA* 1994, **271**, 907–913.
26. Pyrhönen S, Hahka-Kemppainen M, Muhonen T. A promising interferon plus four-drug chemotherapy regimen for metastatic melanoma. *J Clin Oncol* 1992, **10**, 1919–1926.
27. Nathan FE, Berd D, Sato T, *et al.* BOLD + interferon in the treatment of metastatic uveal melanoma: first report of active systemic therapy. *J Exp Clin Cancer Res* 1997, **16**, 201–208.
28. Dorval T, Fridman A, Mathiof C, Powillard P. Interleukin-2 therapy for metastatic uveal melanoma (abstract). *Eur J Cancer* 1992, **28A**, 2087.
29. Atzpodien J, Hänninen E, Kirchner H. Chemoimmunotherapy of advanced malignant melanoma: sequential administration of subcutaneous interleukin-2 and interferon-alpha after intravenous dacarbazine and carboplatin or intravenous dacarbazine, cisplatin, carmustine and tamoxifen. *Eur J Cancer* 1995, **31A**, 876–881.