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Outcomes of adoptive cell transfer with tumor-infiltrating lymphocytes for metastatic melanoma patients with and without brain metastases

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Abstract

Brain metastases cause significant morbidity and mortality in patients with metastatic melanoma. Although adoptive cell therapy (ACT) with tumor-infiltrating lymphocytes (TIL) can achieve complete and durable remission of advanced cutaneous melanoma, the efficacy of this therapy for brain metastases is unclear. Records of patients with M1c melanoma treated with ACT using TIL, including patients with treated and untreated brain metastases, were analyzed. Treatment consisted of preparative chemotherapy, autologous TIL infusion, and high-dose interleukin-2. Treatment outcomes, sites of initial tumor progression, and overall survival were analyzed. Among 144 total patients, 15 patients with treated and 18 patients with untreated brain metastases were identified. Intracranial objective responses (OR) occurred in 28% patients with untreated brain metastases. The systemic OR rates for patients with M1c disease without identified brain disease, treated brain disease, and untreated brain disease, and were 49%, 33% and 33%, respectively, of which 59%, 20% and 16% were durable at last follow-up. The site of untreated brain disease was the most likely site of initial tumor progression (61%) in patients with untreated brain metastases. Overall, we found that ACT with TIL can eliminate small melanoma brain metastases. However, following TIL therapy these patients frequently progress in the brain at a site of untreated brain disease. Patients with treated or untreated brain disease are less likely to achieve durable systemic ORs following TIL therapy compared with M1c disease and no history of brain disease. Melanoma brain metastases likely require local therapy despite the systemic impact of ACT.

Keywords

adoptive cell transfer; brain metastases; cancer immunotherapy; metastatic melanoma; tumor-infiltrating lymphocytes

Introduction

The development of effective immunotherapy, including adoptive cell transfer (ACT) of autologous lymphocytes and checkpoint inhibitors, has dramatically altered the management of metastatic cutaneous melanoma.(1–4) For example, therapy using autologous Tumor Infiltrating Lymphocytes(TIL) has achieved an objective response rate (ORR) of 55% and a complete response (CR) rate of 23% in 194 patients with advanced melanoma treated at the Surgery Branch, National Cancer Institute.(5)

Despite these advances, patients with advanced melanoma and concurrent systemic and intracranial disease present a frequent and difficult clinical challenge. With surgery and radiation therapy, overall survival of patients with melanoma brain metastases is 8.9 months. (6) In many cases tumor multiplicity, or proximity to eloquent structures, precludes safe surgical resection. Stereotactic radiosurgery (SRS) can be used to treat such lesions, but local control is achieved in only 75% of tumors $\leq 2 \text{ cm}^3$ and 42% of tumors $> 2 \text{ cm}^3$.(7) Because systemic immunotherapy offers the potential benefit of simultaneously managing both systemic and intracranial disease, we have used TIL to treat selected patients with metastatic melanoma and untreated brain disease.

Previously we recognized that activated lymphocytes can traffic to the CNS and reported intracranial objective responses to TIL therapy in 7 of 17 patients with untreated melanoma brain metastasis.(8) The objective of this report was to update and extend our prior analysis in a patient population that received a TIL product that was generated from melanoma tumor fragments.(9) This cell production technique is currently used by the Surgery Branch and in ongoing multi-institutional trials evaluating TIL for patients with melanoma (NCT02360579). We analyzed the intracranial and overall systemic response rate, identified the first site of tumor progression when disease progression occurred, and provide long-term outcomes for this cohort of patients. Finally, we also described the outcomes for patients with treated brain metastasis as well as patients with M1C disease with no history of brain disease.

Patients and Methods

Study Population

The NCI Surgery Branch has conducted multiple clinical trials to investigate the efficacy of ACT with autologous TIL given in conjunction with a preparative non-myeloablative conditioning and high-dose IL-2 for patients with advanced melanoma. From 2001 to 2016, 502 patients met protocol eligibility requirements which included age ≥ 18 , ECOG score ≤ 2 , life expectancy of > 3 months, and adequate hepatic, renal, and hematopoietic reserve and were treated with melanoma TIL. Patients had evaluable extracranial disease and were enrolled on NCI IRB-approved clinical trials. From this group, all patients with M1c disease at time of treatment were identified.(10) Patients with a history of treated brain disease were eligible if all lesions were resected or lesions were treated with radiation and documented to be stable for a minimum of 4 weeks. Patients with untreated brain metastasis were eligible if they had ≤ 3 lesions, each measuring $\leq 10 \text{ mm}$ and without significant edema (1 patient had

5 metastases and 2 of these were identified retrospectively). Patients with leptomeningeal disease, intra-axial spinal cord lesions, and those on corticosteroid therapy were excluded. Because our TIL production process had been modified over the 15-year study period and to increase the homogeneity of our study population we included only patients who received a TIL cell product generated from tumor fragments, representing how TIL are currently derived in the Surgery Branch. Patients treated with autologous lymphocytes generated from either a core biopsy or from bulk TIL cultures were excluded, as were patients enrolled as a compassionate exemption. One hundred forty-four patients met our study criteria and were the focus of this analysis. This M1c population was analyzed in 3 cohorts; M1c disease and no history of brain disease, M1c disease with treated brain metastases, and M1c disease with untreated brain metastases.

Treatment

TIL Production—TIL were generated from small tumor fragments obtained from resected melanoma lesions as previously described.(9) In brief, single tumor fragments of 2 mm³ to 3 mm³ were placed in individual wells of a 24-well plate and grown in culture with 6,000 IU/mL IL-2 until a homogenous lymphocyte culture developed. Up to six individual fragment cultures with sufficient growth or autologous tumor reactivity were selected for rapid expansion (REP). These cultures were generally cryopreserved and subsequently thawed 2 days prior to REP. The REP consisted of the TIL culture with OKT3 (anti-CD3) antibody (Milenyi Biotech, San Diego, CA) and IL-2 (3,000 IU/mL; Prometheus, San Diego, CA) in the presence of irradiated feeder cells, autologous when possible, at a 100:1 ratio.

Protocol Design—The general design of our TIL infusion protocols has been previously reported.(4) Eligible patients received a non-myeloablative conditioning regimen that consisted of cyclophosphamide 60 mg/kg/day for 2 days (days -7 and -6 before ACT) and fludarabine 25 mg/m²/day for 5 days (days -7 to -3). On select protocols, total body irradiation (TBI; 200 or 1200 cGy) was added to provide additional lymphodepletion 1 to 3 days before TIL transfer. Patients treated with TBI received an additional infusion of autologous CD34+ hematopoietic stem cells, as previously described. Patient who received TBI were included because a randomized control trial demonstrated no difference when TBI is added to preparative regimen.(5) Following TIL infusion, patients received Interleukin-2 (IL-2) (720,000 IU/kg) every 8 hours as tolerated. Patients with brain disease were closely monitored for thrombocytopenia and transfused as necessary to maintain a platelet count of approximately 20,000 cells/ μ L.

Follow-up

Clinical evaluation including imaging for tumor response was obtained 4 weeks after treatment, and at 4- to 8-week intervals for approximately 2 years. Patients with untreated brain metastasis or a history of brain disease had magnetic resonance imaging (MRI) imaging of the brain, including post-contrast, T1-weighted sequences, at baseline and at each evaluation. For the other M1c patients, brain imaging was typically obtained every 8–12 weeks. Subsequent follow-up included imaging every 6 months for 5 years. Criteria for response were determined using the Response Evaluation Criteria in Solid Tumors

(RECIST) v1.0.(11) For the purpose of this study we reported all brain lesions despite them being 1 cm in diameter. The intracranial response criteria were compatible with the Response Assessment in Neuro-Oncology Brain Metastases (RANO-BM).(12) After progression by RECIST criteria, patients were discharged from their respective Surgery Branch treatment protocols. Therefore, complete data on subsequent treatments were not available.

Statistical methods

Kaplan-Meier analyses were used to determine the progression-free survival (PFS) and overall survival (OS) of different patient cohorts, beginning at the date of cell infusion. The statistical significance of the difference between Kaplan-Meier curves was determined using the log-rank test. Because the comparisons involving the patients without brain metastases were determined in advance, the p-values are reported without adjustment for multiple comparisons. Fisher's exact test was used to compare the response rates and sites of first tumor progression between the cohorts with treated and untreated brain metastases, and between untreated brain metastases and those without brain metastases. All p-values are two-tailed with $p < 0.05$ indicating a statistically significant difference.

Results

Patients and treatment characteristics

One-hundred forty-four patients with M1c metastatic melanoma were treated with TIL and met our study inclusion criteria (Table 1). There were 111 patients with M1c disease and no history of brain disease, 15 patients with treated brain metastases, and 18 patients with untreated brain metastases. Three of the 18 patients with untreated brain disease had been included in our preliminary report.(8) All patients received the planned preparative non-myeloablative chemotherapy. Fifty-six patients (39%) received total body irradiation before cell infusion. Although more patients without brain metastases received TBI than patient with treated or untreated brain metastases, the addition of TBI has not been demonstrated to improve the rate or duration of response.(5) The number of IL-2 doses appeared to be similar in the 3 cohorts (Table 1). One patient with an untreated brain metastasis did not receive IL-2 because of immediate toxicity related to the cell infusion. Two patients without brain metastases had received prior ACT with TIL. Median follow-up was 1.1 years for all patients (range 0.1 to 13.5 years).

Of the 15 patients with treated brain disease, 6 had received SRS, 7 had previously undergone surgery, and 2 had both prior to cell therapy. In addition, one patient had whole brain radiation therapy after local SRS. Among the 18 patients with untreated brain metastases, multiple metastases were identified in 8 patients (44%). All untreated tumors measured 10 mm in maximum diameter, 3 lesions and the median size of the largest untreated metastasis was 6 mm. Three of these 18 patients had received prior treatment for brain metastasis and had subsequently developed new brain lesions prior to ACT.

Intracranial responses

Objective responses of brain metastases were identified in 5 of the 18 patients with untreated brain metastases (28%; Table 2). Four of these were complete responses (CRs)(Figure 1) and one intracranial response was partial (PR). This PR was observed in a patient with 3 untreated brain metastases, with 2 lesions completely regressing and 1 lesion diminished in size but clearly present at last follow-up (5 months post ACT). Although these intracranial responses were all durable, 1 of these patients developed new sites of brain disease 4 months after ACT. Of the remaining 13 patients, 10 developed progression of a known metastasis and 3 were noted to have stable brain disease at last follow-up. The individuals with stable brain disease developed rapid tumor progression at non-brain sites and were discharged from protocols at the NCI. One patient with 3 untreated brain metastases at the time of ACT demonstrated a mixed response, consisting of simultaneous progression of one lesion, a new lesion and regression of others (Figure 2). Among the 10 patients with progression, 4 underwent surgical resection, 2 underwent SRS, 3 underwent whole-brain radiation therapy (WBRT), and 1 underwent SRS followed by WBRT.

Brain metastasis-associated complications

Intracranial complications of ACT in the cohort with untreated brain metastases were limited to tumor-associated hemorrhage after treatment. A small tumor-associated hemorrhage was detected in one patient at the initial 4-week post-treatment evaluation. This patient remained asymptomatic and was managed conservatively. A second patient developed symptomatic intracerebral frontal lobe hemorrhage 4 days after TIL infusion and required a craniotomy for clot evacuation and tumor resection. Pathologic analysis of this specimen identified viable melanoma. This patient suffered a hemiparesis and rapid disease progression which included new brain metastasis. The platelet nadirs for the 2 patients with tumor-associated hemorrhage were within the protocol target goal (36,000 and 20,000 cell/ μ L, respectively). Of note, with the exception of the patient with the symptomatic intracerebral hemorrhage, there was no IL-2 or cell related grade 3 or 4 neurotoxicity noted in the patients with untreated brain disease.

Overall responses

The overall systemic objective response (OR) rates are noted in Table 3. Patients with M1c melanoma without brain metastases achieved an OR rate of 49% (PR 28%, CR 21%). Five of 15 patients (33%) with treated brain metastases and 6 of 18 patients (33%) with untreated brain metastases achieved an OR. Only one patient with a history of brain disease and no patient with active brain disease developed a CR (Figure 2). Of the 33 patients with treated or untreated brain metastases, only 1 patient had an ongoing systemic response at last follow up. Overall, the OR rates between the groups were not statistically significant (Fisher's exact test).

First site of tumor progression

Of the 144 M1c patients, 109 (76%) developed tumor progression and 35 (24%) sustained an OR. The site(s) of first progression was identified for the 109 patients with disease progression and are noted in Table 4. Patients with untreated brain disease were more likely

to progress first in the brain than patients without brain metastases (Fisher's exact test, $P < 0.0001$) and patients with treated brain metastases ($P = 0.03$). Patients with untreated brain metastases were most likely to progress first at the site of the untreated disease (56%). Of the 17 patients with untreated brain metastases who ultimately developed PD, 5 patients initially progressed only at extracranial sites. Patients without brain metastases and with treated brain metastases appeared to be at similar risk for developing new brain disease. No brain lesion treated with radiation showed tumor progression.

Progression-free and overall survival

The PFS for each of the 3 study cohorts is documented in Figure 3A. Patients without brain metastases achieved longer PFS than patients with untreated brain metastases (log-rank, $P = 0.004$). This fact reflected the proclivity for untreated brain metastasis to progress and to require additional treatment following ACT with TIL. Although patients without brain metastases also achieved longer PFS than patients with treated brain metastases, this difference was not significant ($p = 0.11$). The OS for our study population is noted in Figure 3B. Patients without brain metastases achieved longer OS than patients with untreated brain metastases following ACT therapy with TIL (log-rank, $P = 0.02$). The OS for patients with treated brain disease and untreated brain disease was not significantly different ($p = 0.47$). Three patients (17%) with untreated brain metastases were alive at last follow-up. These included one patient with an ongoing overall and intracranial partial response, one patient with a complete intracranial response who is now free of disease after metastasectomy of a progressive omental mass, and one patient with no disease following a craniotomy for an enlarging metastasis.

Discussion

Brain metastases are a frequent cause of morbidity and mortality for patients with advanced melanoma. Surgery and/or radiation are standard therapy for this disease, but median survival using these modalities remains limited.(6) Immunotherapy with check point inhibitors and ACT have gained recent recognition as effective and durable treatments for patients with metastatic melanoma. These therapies have made it possible in selected patients to simultaneously treat both cranial and extra-cranial disease sites. Unfortunately, it has been difficult to quantify the overall efficacy of these treatments for patients with brain disease. Multi-center trials of immune checkpoint inhibitors targeting cytotoxic T lymphocyte antigen-4 (CTLA-4), programmed cell death protein 1 (PD-1), and programmed death-ligand 1 (PD-L1) have generally excluded patients with untreated brain metastases.(1–3) Weber and colleagues retrospectively analyzed the results of CTLA-4 inhibition (ipilimumab) in 12 patients with stable (non-growing) brain metastases at the time of treatment and observed 2 partial responses (16%).(13) Margolin and colleagues prospectively enrolled 72 patients with untreated brain metastases in a trial of ipilimumab and reported 1 CR and 8 PRs for an ORR of 13%.(14) Goldberg and colleagues reported the results of 18 patients with melanoma brain metastases (up to 3 cm) treated with pembrolizumab and identified partial responses in 4 patients and that were sustained between 4 to 10 months at the last evaluation.(15) Two more recent reports have noted promising results with the use of Nivolumab plus Ipilimumab. Tawbi *et al.* reported 16 CRs

and 25 PRs of intracranial disease in 75 patients with melanoma brain metastasis treated with combination therapy. The overall systemic ORR was 53% in this population.(16) Long *et al.* noted an intracranial response rate of 42% and an overall 6 month PFS of 46% in a similar cohort of 26 patients treated with Nivolumab plus Ipilimumab.(17) Although it appears both intracranial and extracranial disease regression can be durable, long term follow up has not yet been reported.

Adoptive cell transfer (ACT) with tumor-infiltrating lymphocytes is capable of mediating objective responses in over 50% of patients and durable CRs in 22% of patients with advanced melanoma.(4) This strategy is now the focus of at least 20 ongoing clinical trials. We have previously reported that melanoma TIL can effectively traffic to the CNS and noted complete intracranial responses in 7 of 17 patients with melanoma brain metastasis.(8) We now report a more focused analysis that included only patients with untreated brain disease who received TIL that were generated from small tumor fragments. We provide longer and more complete follow up and outcome data. In addition, we compared the clinical outcome of TIL treatment of patients that had untreated brain disease with patients that had treated brain metastasis and with patients with no prior history of brain disease.

Five of 18 patients treated with TIL achieved an intracranial response and four of these were CRs. Although this response rate is lower than we previously reported, this is likely a consequence of the small sample size and different patient eligibility criteria in both analyses. Brain-specific treatment-associated toxicity was limited to tumor-associated hemorrhage in 2 of the 18 patients. Such hemorrhages did not appear to be specifically related to the platelet nadir associated with the lymphodepleting chemotherapy. These findings support continuing a management paradigm of maintaining a goal platelet count of 20,000 cells/ μ L, when untreated brain metastases are present.

The PFS for patients with untreated brain disease was significantly shorter than for patients with no history of brain disease. This observation was a consequence of the fact that of the 17 patients with untreated CNS disease that developed tumor progression, 10 patients progressed rapidly at a site of untreated brain disease and 2 progressed with new brain disease. Interestingly, the risk of intracranial progression in patients with treated brain metastasis was not statistically different than in those patients with no history of brain disease. This may have been the result of the eligibility requirement that patients with treated brain disease must have had at least 1 month of stable brain disease prior to protocol entry.

The systemic response rate and overall survival analysis yielded important insights. As noted in Table 3, there was no statistical difference in the OR rate in the 3 cohorts analyzed. However, it is noteworthy that only 1 of the 15 patients with treated brain disease and none of the 18 patients with untreated brain metastasis achieved a CR. Moreover, the durability of the objective responses in patients with untreated and treated brain metastasis was decreased compared with patients with M1C disease and no history of brain disease (Table 3). Only 1 of the 18 patients with untreated brain disease and 1 of the 15 patients with a treated brain metastasis had ongoing objective responses at last evaluation. Interestingly both patients had partial responses. While there was no statistically significant difference in OS between

patients with treated or untreated brain metastases, likely due to low power ($P = 0.11$), patients with untreated brain disease had lower OS than patients with M1c disease without brain disease, ($P = 0.02$) (Figure 3B). Of note, as complete data on subsequent therapies after progression following ACT were not available, OS data in this study were limited by potentially heterogeneous additional treatments.

Taken together, our experience with ACT to treat melanoma brain metastasis confirmed that TIL can traffic to the brain and safely mediate the complete and durable regression of brain disease for some patients with limited brain metastasis. Unfortunately, we also found that most patients with untreated brain disease required additional brain-directed therapy following TIL treatment. Furthermore, patients with melanoma brain metastasis suffered reduced overall survival compared to patients with M1C disease without CNS involvement. Patients with small asymptomatic melanoma brain disease may safely receive treatment with TIL followed by brain directed therapy as needed, however establishing local control of brain disease prior to ACT also appears to be an acceptable therapeutic strategy. The presence of brain disease should be factored into the interpretation and design of clinical trials for patients with advanced melanoma. It is noteworthy that effective January 2018, the American Joint Committee on Cancer will include patients with advanced melanoma and CNS involvement as Stage M1D. (18)

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References

1. Hodi FS, O'Day SJ, McDermott DF, Weber RW, Sosman JA, Haanen JB, et al. Improved survival with ipilimumab in patients with metastatic melanoma. *N Engl J Med*. 2010; 363:711–23. [PubMed: 20525992]
2. Topalian SL, Sznol M, McDermott DF, Kluger HM, Carvajal RD, Sharfman WH, et al. Survival, durable tumor remission, and long-term safety in patients with advanced melanoma receiving nivolumab. *J Clin Oncol*. 2014; 32:1020–30. [PubMed: 24590637]
3. Brahmer JR, Tykodi SS, Chow LQM, Hwu W-J, Topalian SL, Hwu P, et al. Safety and activity of anti-PD-L1 antibody in patients with advanced cancer. *N Engl J Med*. 2012; 366:2455–65. [PubMed: 22658128]
4. Rosenberg SA, Yang JC, Sherry RM, Kammula US, Hughes MS, Phan GQ, et al. Durable Complete Responses in Heavily Pretreated Patients with Metastatic Melanoma Using T-Cell Transfer Immunotherapy. *Clin Cancer Res*. 2011; 17:4550–7. [PubMed: 21498393]
5. Goff SL, Dudley ME, Citrin DE, Somerville RP, Wunderlich JR, Danforth DN, et al. Randomized, Prospective Evaluation Comparing Intensity of Lymphodepletion Before Adoptive Transfer of Tumor-Infiltrating Lymphocytes for Patients With Metastatic Melanoma. *J Clin Oncol*. 2016; 34:2389–97. [PubMed: 27217459]
6. Fife KM, Colman MH, Stevens GN, Firth IC, Moon D, Shannon KF, et al. Determinants of outcome in melanoma patients with cerebral metastases. *J Clin Oncol*. 2004; 22:1293–300. [PubMed: 15051777]

7. Selek U, Chang EL, Hassenbusch SJ, Shiu AS, Lang FF, Allen P, et al. Stereotactic radiosurgical treatment in 103 patients for 153 cerebral melanoma metastases. *Int J Radiat Oncol Biol Phys*. 2004; 59:1097–106. [PubMed: 15234044]
8. Hong JJ, Rosenberg SA, Dudley ME, Yang JC, White DE, Butman JA, et al. Successful Treatment of Melanoma Brain Metastases with Adoptive Cell Therapy. *Clin Cancer Res*. 2010; 16:4892–8. [PubMed: 20719934]
9. Dudley ME, Wunderlich JR, Shelton TE, Even J, Rosenberg SA. Generation of tumor-infiltrating lymphocyte cultures for use in adoptive transfer therapy for melanoma patients. *J Immunother*. 2003; 26:332–42. [PubMed: 12843795]
10. Compton, CC.Byrd, DR.Garcia-Aguilar, J.Kurtzman, SH.Olawaiye, A., Washington, MK., editors. *AJCC Cancer Staging Atlas*. New York, NY: Springer New York; 2012.
11. Therasse P, Arbuck SG, Eisenhauer Ea, Wanders J, Kaplan RS, Rubinstein L, et al. New guidelines to evaluate the response to treatment in solid Tumors. *JNatlCancer Inst*. 2000; 92:205–16.
12. Lin NU, Lee EQ, Aoyama H, Barani IJ, Barboriak DP, Baumert BG, et al. Response assessment criteria for brain metastases: proposal from the RANO group. *Lancet Oncol*. 2015; 16:e270–8. [PubMed: 26065612]
13. Weber JS, Amin A, Minor D, Siegel J, Berman D, O'Day SJ. Safety and clinical activity of ipilimumab in melanoma patients with brain metastases: retrospective analysis of data from a phase 2 trial. *Melanoma Res*. 2011; 21:530–4. [PubMed: 22051508]
14. Margolin K, Ernstoff MS, Hamid O, Lawrence D, McDermott D, Puzanov I, et al. Ipilimumab in patients with melanoma and brain metastases: An open-label, phase 2 trial. *Lancet Oncol Elsevier Ltd*. 2012; 13:459–65.
15. Goldberg SB, Gettinger SN, Mahajan A, Chiang AC, Herbst RS, Sznol M, et al. Pembrolizumab for patients with melanoma or non-small-cell lung cancer and untreated brain metastases: early analysis of a non-randomised, open-label, phase 2 trial. *Lancet Oncol Elsevier Ltd*. 2016; 17:976–83.
16. Tawbi HA-H, Forsyth PAJ, Algazi AP, Hamid O, Hodi FS, Moschos SJ, et al. Efficacy and safety of nivolumab (NIVO) plus ipilimumab (IPI) in patients with melanoma (MEL) metastatic to the brain: Results of the phase II study CheckMate 204. *J Clin Oncol American Society of Clinical Oncology*. 2017; 35:9507.
17. Long GV, Atkinson V, Menzies AM, Lo S, Guminski AD, Brown MP, et al. A randomized phase II study of nivolumab or nivolumab combined with ipilimumab in patients (pts) with melanoma brain metastases (mets): The Anti-PD1 Brain Collaboration (ABC). *J Clin Oncol American Society of Clinical Oncology*. 2017; 35:9508.
18. Amin, MB., Edge, S., Greene, F., Byrdm, DR., et al. *AJCC Cancer Staging manual*. 8. Springer; 2017.

Figure 1.

Complete response of an untreated melanoma brain metastasis to adoptive cell therapy with tumor-infiltrating lymphocytes (TIL). A) One-month pre-treatment and B) immediate pre-treatment axial, T1-weighted, post-contrast magnetic resonance imaging (MRI) demonstrate a growing right temporal brain metastasis (white arrowhead). C) One month after adoptive cell therapy with TIL, lesion diameter was reduced by greater than 50%. D) The lesion was eradicated by two months after treatment and was not visualized on most-recent follow-up imaging 9 years after treatment (pictured).

Figure 2.

Mixed response in a patient with multiple untreated melanoma brain metastases after adoptive cell therapy (ACT) with tumor-infiltrating lymphocytes (TIL). A) Pre-treatment axial, T1-weighted, post-contrast magnetic resonance imaging (MRI) demonstrates 2 untreated right frontal brain metastases in a patient with metastatic melanoma. B) Three months after ACT with TIL a complete response was observed in the anterior lesion, whereas the posterior lesion had progressed necessitating surgical management. An additional 5 mm left temporal brain metastasis progressed as well, also requiring surgery (not pictured).

Figure 3.

Kaplan-Meier analyses of progression-free survival (PFS; all tumor sites) and overall survival (OS) in 144 stage M1c patients treated with adoptive cell therapy (ACT) with tumor-infiltrating lymphocytes (TIL) and stratified by the presence of previously-treated or untreated brain metastases. A) PFS in patients treated with TIL. Comparison of PFS in patients with untreated brain metastases and stage M1c patients without brain metastases demonstrates significantly greater PFS in the cohort without brain lesions (log-rank, $P=0.004$). The difference in PFS between patients with treated brain metastases and stage M1c patients without brain metastases was not significant (log-rank, $P=0.11$). B) OS in patients treated with TIL. Comparison of OS in patients with untreated brain metastases and stage M1c patients without brain metastases demonstrates significantly greater OS in the cohort without brain lesions (log-rank, $P=0.02$). The difference in OS between patients with treated brain metastases and stage M1c patients without brain metastases was not significant (log-rank, $P=0.11$).

Table 1

Baseline characteristics of 144 patients treated with tumor infiltrating lymphocytes.

Variable	Stage M1c - no brain metastases (n=111)	Stage M1c - treated brain metastases (n=15)	Stage M1c -untreated brain metastases (n=18)
Age at treatment (median [range], years)	47 (18–68)	46 (25–59)	43 (24–64)
Females	40 (36%)	6 (40%)	5 (28%)
Prior treatment for brain metastases	-	15 (100%)	3 (17%)
Untreated brain metastases (median [range])	-	-	1 (1 to 5)
Multiple brain metastases	-	-	8 (44%)
Size of largest brain metastasis (median [range], mm.)	-	-	6 (2 to 10)
Total body irradiation	48 (43%)	3 (20%)	5 (28%)
200 cGy	10	0	2
1200 cGy	38	3	3
Cell dose (median [range], $\times 10^9$ cells)	69 (9–108)	52 (31–137)	51 (10–109)
Interleukin-2 doses (median [range])	6 (1–15)	8 (4–12)	6 (0–10)

Table 2

Intracranial and overall outcomes in 18 patients with untreated brain metastases treated with tumor infiltrating lymphocytes.

Outcome	Number (%)	Individual patient overall responses (duration in months)
Objective response	5 (28)	
Partial response	1 (6)	PR (5+)
Complete response	4 (22)	PR (4), PR (4), PD, PD
Progressive disease	10 (56)	PR (9), PR (4), PD, PD, PD, PD, PD, PD, PD, PD
Mixed responses *	1 (6)	
Symptomatic hemorrhage	1 (6)	
Stable disease	3 (16)	PR (8), PD, PD

* Tumors with progression and regression in same patient

PR = partial response

PD = progressive disease

+ = ongoing response

Table 3

Overall responses in 144 patients treated with tumor infiltrating lymphocytes. *

Outcome	Stage M1c - no brain metastases (n=111)	Stage M1c - treated brain metastases (n=15)	Stage M1c - untreated brain metastases (n=18)
Progressive disease	56 (50%)	10 (67%)	12 (67%)
Stable disease	1 (1%)	0 (0%)	0 (0%)
Partial response	31 (28%)	4 (26%)	6 (33%)
Ongoing	10	1	1
Complete response	23 (21%)	1 (7%)	0 (0%)
Ongoing	22	0	0

*
by RECIST criteria

Table 4

Site of progression in 144 patients treated with tumor infiltrating lymphocytes.

Outcome	Stage M1c - no brain metastases (n=111)	Stage M1c - treated brain metastases (n=15)	Stage M1c -untreated brain metastases (n=18)
No progression at last follow-up	33 (30%)	1 (7%)	1 (6%)
Progressed *	78 (70%)	14 (93%)	17 (94%)
Site of initial progression:			
Extracranial sites only	68	10	5
Intracranial and extracranial sites	7	0	3
Intracranial sites only	3	4	9
At the untreated intracranial site	-	-	10

* Includes patients with an initial treatment response