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Original Research

Long term survival with cytotoxic T lymphocyte-associated antigen 4 blockade using tremelimumab

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Abstract ***Purpose:*** One of the hallmarks of cancer immunotherapy is the long duration of responses, evident with cytokines like interleukin-2 or a variety of cancer vaccines. However, there is limited information available on very long term outcomes of patients treated with anti-cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) antibodies. Tremelimumab is an anti-CTLA-4 antibody of immunoglobulin G2 (IgG2) isotype initially tested in patients with advanced melanoma over 12 years ago.

Methods: We reviewed the outcomes of patients with advanced melanoma enrolled in four phase 1 and 2 tremelimumab trials at two sites to determine response rates and long-term survival.

Results: A total of 143 patients were enrolled at two institutions from 2002 to 2008. Tremelimumab administration varied between a single dose of 0.01 mg/kg and 15 mg/kg every 3 months. Median overall survival was 13 months (95% confidence interval (CI), 10–16.6),

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ranging from less than a month to 12+ years. An objective response rate of 15.6% was observed, with median duration of response of 6.5 years, range of 3–136+ months. The Kaplan–Meier estimated 5 year survival rate was 20% (95% CI, 13–26%), with 10 and 12.5 year survival rates of 16% (95% CI, 9–23%).

Conclusions: CTLA-4 blockade with tremelimumab can lead to very long duration of objective anti-tumour responses beyond 12 years.

1. Introduction

A well-recognised hallmark of cancer immunotherapy is the long duration of responses, lasting even decades, as evidenced with the use of high dose interleukin-2 or certain cancer vaccines [1,2]. Only a minority of patients with advanced melanoma attain objective responses with these therapies; however, when reached, the nature of these responses is usually sustained over several years.

Anti-cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) antibodies such as ipilimumab and tremelimumab bind to the inhibitory CTLA-4 receptor on T cells; by blocking the inhibition of co-stimulatory B7 ligands by CTLA-4, they increase immune stimulation and drive T cell activity [3]. Both drugs are fully human monoclonal antibodies directed against CTLA-4; there are minimal differences between them as ipilimumab is an immunoglobulin G1 (IgG1) isotype and tremelimumab is a non-complement-fixing immunoglobulin G2 (IgG2) isotype [4]. Ipilimumab was approved by the FDA in 2011 for the treatment of patients with unresectable metastatic melanoma based on improvement in overall survival (OS) in two randomised trials [5,6]. While response rates for ipilimumab in patients with advanced melanoma have ranged from only 10–15% [6], the demonstration of long-lasting responses with ipilimumab has stimulated further interest in use of these therapies, with a plateau in the survival curve of 21% beginning at 3 years [7].

As the other anti-CTLA-4 antibody in clinical trials, tremelimumab has also been studied in patients with advanced melanoma and other tumour types [10]. A phase 2 trial of tremelimumab in melanoma compared two dosing regimens at 10 mg/kg once per month and 15 mg/kg once every 3 months [11]. While no difference was seen in the response rate or survival, a dose of 15 mg/kg every 3 month dosing was selected for phase 3 trial testing due to a better toxicity profile. In the phase 3 trial, 655 patients with Stage IIIC or IV and measurable disease were enrolled and randomised to either tremelimumab at 15 mg/kg every three months or chemotherapy with dacarbazine or temozolamide. While no significant statistical differences were observed in the overall response rates (11% with tremelimumab and 10% with chemotherapy; $p = 0.618$) or median OS (12.6 months for tremelimumab and 10.7 months with chemotherapy; $p = 0.127$) between arms, the duration of the anti-tumour responses was significantly different (tremelimumab 35.8 months versus chemotherapy 13.7 months ($p = 0.0011$) [12]. The study design did not allow crossover for patients who progressed to chemotherapy. However, patients in the chemotherapy arm were exposed to ipilimumab (up to 34% of patients who were alive or censored at time of study closure) and the cross-over therapy with the frequent use of a different anti-CTLA-4 antibody in the chemotherapy control arm may have explained the lack of a survival impact [13].

Newer immune checkpoint inhibitors such anti-PD-1 and PD-L1 antibodies have shown response rates ranging between 30% and 40%, higher than either of the two anti-CTLA-4 antibodies, although long term follow up of patients treated with anti-PD-1/PD-L1 therapies is not yet available [14,15]. As both ipilimumab and tremelimumab have moved towards combination regimens in clinical trials with other checkpoint inhibitors or immune agonists in advanced melanoma and other tumours [16,17], we wanted to evaluate the long-term survival in patients with advanced melanoma treated with tremelimumab. We retrospectively reviewed the records of 143 patients enrolled in four different phase 1 and 2 tremelimumab trials and report on the outcome and follow up of those patients during the past decade.

2. Methods

2.1. Patients

The data presented in this retrospective analysis were obtained from patients enrolled in four clinical trials conducted at University of California, Los Angeles (UCLA) and MD Anderson Cancer Center since these two sites were the initial and highest accruing sites for the early tremelimumab clinical trials. All patients with confirmed stage IIIC or IV melanoma were included. Further details can be found in the original publications of each of the studies [11,18–20]. The Institutional Review Boards of both participating institutions approved all trials and signed informed consent was obtained from every study participant.

The first trial analysed was the phase 1 study of tremelimumab, which enrolled 34 patients with advanced melanoma from UCLA and MD Anderson from January 2002 until August 2003 [18]