Immunobiology 217 (2012) 583–589

Contents lists available at ScienceDirect

Immunobiology

journal homepage: www.elsevier.de/imbio

Review

Ipilimumab (Yervoy) and the TGN1412 catastrophe

Tibor Bakacs[a], Jitendra N. Mehrishi[b,*], Ralph W. Moss[c]

[a] Department of Probability, Alfred Renyi Institute of Mathematics, Hungarian Academy of Sciences, Realtanoda utca 13-15, H-1053 Budapest, Hungary
[b] University of Cambridge, United Kingdom
[c] Cancer Decisions, P.O. Box 1076, Lemont, PA 16851, United States

ARTICLE INFO

Article history:
Received 7 May 2011
Accepted 3 July 2011

Keywords:
Ipilimumab
Yervoy
Anti-CTLA-4 monoclonal antibody
TGN1412
Anti-CD28 monoclonal antibody
Regulatory T cells
Breakdown of tolerance

ABSTRACT

The development of the anti-CTLA-4 antibody (ipilimumab; marketed as Yervoy[1]) immune regulatory therapy was based on the premise that "Abrogation of the function of CTLA-4 would permit CD28 to function unopposed and might swing the balance in favor of immune stimulation, tolerance breakdown and tumor eradication…" (Weber, 2009). By now, the vast majority of data collected from more than 4000 patients proves that this prediction was entirely correct. Paradoxically, the successful blockade of immune checkpoints raises the question whether an anti-CTLA-4 antibody could ever become an important therapy against cancer.

T cells lost their ability to discriminate between self and non-self. Thus, tolerance to self tissues was broken in ~70% of the patients. In the recent industry-sponsored phase III clinical trial of ipilimumab, 147 (38.7%) of the patients experienced severe adverse events and 6.8% suffered dose-limiting events (8.4%, in the ipilimumab-alone group). There were 14 deaths related to the study drugs and 7 of these were associated with immune-related adverse events. In contrast, the complete response rate was only 0.2%, in one patient out of 403 who received ipilimumab plus a peptide vaccine.

Promoters of ipilimumab appear to be unmindful of the clinical trial catastrophe in London. Then, a humanized "superagonist" anti-CD28 monoclonal antibody, TGN1412, which "preferentially" activated regulatory T cells, at a higher dose, also activated all CD28 positive T cells. This precipitated a "cytokine storm" leading to life-threatening multiple organ failure in the six healthy human volunteers. Neither anti-CD28 nor anti-CTLA-4 therapies rely on antigen-specificity. Both release free antibody into the body against common molecular targets that are expressed on the targeted as well as on the non-targeted T cells. At lower antibody doses specific T cells are preferentially activated. With increasing antibody dose, however, the kinetics of the interaction is pushed in favor of widespread non-specific T cell expansion.

Using the law of mass action we calculated that the vast majority of the CTLA-4 receptors on all activated T cells (including melanoma specific T cells) in the phase III clinical trial of ipilimumab will have been saturated. This would explain the runaway immune response observed. The conclusions drawn by the authors of the ipilimumab trial paper could bear an independent inspection and reassessment concerning the validation of the blockade of immune checkpoints as an important therapeutic strategy against cancer.

Contents

Abbreviations: APC, antigen-presenting cell; CTLA-4, cytotoxic T lymphocyte-associated antigen-4; gp100, glycoprotein 100; irAEs, immune-related adverse events; mAbs, monoclonal antibodies; MHC, major histocompatibility complex; TCR, T cell receptor; Treg, regulatory T cells; SIV, simian immunodeficiency virus; Siglecs, sialic acid-recognizing Ig-superfamily lectins.

* Corresponding author. Present address: The Cambridge Blood Cell, Stem Cells, Spermatozoa and Opioid Research Initiatives-Blood Doping and High Altitude Res. Macfarlane Cl. 13, Impington, Cambridge CB24 9LZ, United Kingdom. Tel.: +44 1223 57 36 28.
E-mail addresses: bakacs.tibor@upcmail.hu (T. Bakacs), jm45@cam.ac.uk (J.N. Mehrishi), ralphwmoss@gmail.com (R.W. Moss).

[1] Yervoy is an FDA approved human anti-CTLA-4 monoclonal antibody developed by Bristol-Myers Squibb.

0171-2985/$ – see front matter © 2011 Elsevier GmbH. All rights reserved.
doi:10.1016/j.imbio.2011.07.005

Introduction

In past years many new cancer treatments have been promoted as potential cures. The latest one is ipilimumab, which blocks cytotoxic T lymphocyte antigen 4 (CTLA-4) in order to potentiate an antitumor T-cell response. Ipilimumab improved survival of metastatic melanoma patients in a phase III clinical trial, which was reported by the *NEJM* (Hodi et al. 2010). The publication of the results in the academic journal was coincidentally accompanied by reports in the news media of a so-called "seismic shift in cancer"[2]. Dr. Steven O'Day, the lead researcher of the NEJM study (Hodi et al. 2010), for example, claimed that the drug had already shifted the way doctors and patients think about melanoma treatment.

While we are keen to encourage innovative new treatments, frequent past failures justify some skepticism about such claims. For example, this trial (Hodi et al. 2010) reported a response rate of 10.9% in 676 patients administered ipilimumab. But, sadly, this obscured the findings that the complete response rate was in fact (i) only 0.2% with one patient out of 403 who received ipilimumab plus a peptide vaccine, gp100, and (ii) only 1.5% with two patients out of 137 in those receiving ipilimumab alone. The partial response rate was 5.5% in the combined treatment group and 9.5% in the ipilimumab-alone group. This is hardly indicative of a 'seismic shift' in outcomes.

Although there is no reason to doubt that some patients benefited greatly, the impact on overall survival of the patients as a whole was clearly rather small. Patients who received the ipilimumab had a median survival of 10.1 months, compared with 6.4 months in those receiving gp100 alone. Thus, there was a median survival benefit of 3.7 months. (One cannot be certain as to how the patients would have fared with best supportive care alone, as there was no such control group included in the study).

Meanwhile, practically all the patients suffered toxicity. Although an unknown number of the adverse events could have been caused by the disease itself, many were caused by the treatment. This emerges from the adverse-event profile of ipilimumab in the NEJM study (Hodi et al. 2010), which is consistent with that reported in phase 2 trials. The majority of the adverse events were immune-related (irAEs) and consistent with the proposed mechanism of action of ipilimumab. Furthermore, immune-related events occurred in approximately 60% of the patients treated with ipilimumab, compared to only 32% of the patients treated with gp100. The frequency of grade 3 or 4 immune-related adverse events was 10–15% in the ipilimumab groups, while it was only 3.0% in the gp100-alone group. We do not know what it might have been without any treatment, but presumably, it would have been less than 3.0%. All immune-related events occurred during the induction and reinduction periods; the immune-related adverse events most often affected the skin and gastrointestinal tract. The median time to the resolution of immune-related adverse events of grade 2, 3, or 4 was 6.3 weeks (95% CI, 4.3–8.4) in the ipilimumab-plus-gp100 group, 4.9 weeks (95% CI, 3.1–6.4) in the ipilimumab-alone group, and 3.1 weeks (95% CI, 1.1 to not reached) in the gp100-alone group.

Particularly disturbing is the number of grade 3 and grade 4 events. Thus, 147 (38.7%) of the patients experienced severe events and 6.8% suffered dose limiting events (8.4%, in the ipilimumab-alone group). According to the authors (Hodi et al. 2010), there were 14 deaths related to the study drugs and 7 of these were associated with immune-related adverse events. Thus, we conclude that ipilimumab is a drug that may shrink tumors and even extend survival in a minority of patients, while causing severe or dose limiting toxicity in a larger percentage of patients.

Is the benefit of ipilimumab (Yervoy) great enough to warrant its high risk of harm?

Given such poor outcomes of ipilimumab therapy associated with widespread toxicity, the great optimism expressed in the media seems to stretch the point a bit too far. Since the most fundamental principle of medicine in all situations affecting patients is that physicians must do no harm (DeAngelis and Fontanarosa, 2010), we would like to ask here whether the lives extended justify the lives that might have been ended prematurely by taking ipilimumab?

This is a particularly sensitive issue in the context of advanced cancer, defined as an incurable disease. The American Society of Clinical Oncology (ASCO) recently stated (Peppercorn et al. 2011) that "despite many advances, the fact remains that in the vast majority of cases, [targeted] interventions control disease by months, rather than years, and efficacy measured in terms of disease response or time-to-progression does not always translate into improvement in patient quality of life or survival." To this end, ASCO recommended that oncologists should feel no obligation to provide an intervention that clinical evidence and the clinician's best judgment suggest will provide no meaningful benefit to the patient and may cause harm instead.

The primary objective of the present paper therefore is to start a scientific debate about the safety, efficacy and feasibility of a CTLA-4 blockade therapy.

Here, we wish to demonstrate that (i) in spite of appearances[3], the underlying basic mechanism of actions of agonistic (anti-CD28) and inhibitory (anti-CTLA-4) immune modulatory therapies are similar such that they cannot be restricted to the targeted T cell population; and therefore (ii) the long lasting objective of cancer regression can be achieved only with a high risk that tolerance to

[2] http://www.msnbc.msn.com/id/37514210/ns/health-cancer/.

[3] E.g. healthy individuals vs. cancer patients were included in the TGN1412 and ipilimumab trials, respectively; TGN1412 is a potent stimulatory molecule, whereas ipilimumab has very few effects upon T cells in vitro; single vs. multiple dosing; cytokine storm has not been observed with ipilimumab, etc.