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Brentuximab vedotin for steroid-refractory chronic graft-versus-host disease – a phase I study

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Zachariah DeFilipp and colleagues at Massachusetts General Hospital, Boston, MA, USA, conducted a phase I study of brentuximab vedotin (BV) for steroid-refractory (SR) chronic graft-versus-host disease (GvHD) after allogeneic hematopoietic stem cell transplantation. BV is an antibody-drug conjugate which selectively targets activated lymphocytes expressing CD30 antigen. CD30 was assessed in previous studies and was found as a potential biomarker for acute GvHD.

The aim of this phase I study was to assess the maximum tolerated dose and the overall treatment response of BV in SR chronic GvHD patients (n = 19; median age = 59 years, range 23–74). Escalating doses of BV were administered in a modified 3 + 3 design, beginning with 0.3 mg/kg every 3 weeks (dose level −1), 0.6 mg/kg every 3 weeks (dose level 0), 0.9 mg/kg every 3 weeks (dose level +1), 1.2 mg/kg every 3 weeks (dose level +2), 1.5 mg/kg every 3 weeks (dose level +3), and 1.8 mg/kg every 3 weeks (dose level +4). In total, three patients received BV at a dose level, starting with dose level 0. If there were no DLTs occurring, the patient received the next dose level BV in 21-day cycles for up to 16 cycles of therapy.

Key findings:

Safety

- Therapy discontinuation occurred due to toxicities (n = 9), patient decision (n = 3), lack of response (n = 2), and death (n = 1)
- Dose-limiting toxicities observed on study included posterior reversible encephalopathy syndrome (cohort 4, grade 3) and sepsis (cohort 4, grade 4)
- The maximum tolerated dose was not reached because the trial was prematurely closed due to toxicity
- The most common (≥ 20%) treatment-emergent adverse events (AEs) were fatigue (35%), hypertension (24%), peripheral neuropathy (24%), and upper respiratory infection (24%)
- Grade 3–4 non-hematologic AEs that were attributed to therapy occurred in 7 patients (41%)
    - These AEs were peripheral neuropathy (n = 4), rash (n = 1), posterior reversible encephalopathy syndrome (n = 1), and sepsis (n = 1)
    - Development of moderate or severe peripheral neuropathy led to termination of therapy in each of the four cases

Efficacy

- Eight patients (47%) achieved a partial response, nine patients (53%) had a lack of response

- No complete responses were observed
- Eleven patients (65%) received reduced doses of systemic corticosteroid treatment by ≥ 50% by 6 months after initiation of BV, moreover, three patients discontinued corticosteroids
- Median soluble CD30 level before therapy: 61.5 ng/mL (range, 7.8–9)
- There was no significant association between soluble CD30 level and cGvHD severity at enrollment or clinical responses to BV

The study group concluded that "BV may have activity in treatment of steroid-refractory cGvHD, yet its use is limited by treatment-emergent toxicities, including peripheral neuropathy." The authors added that for chronic GvHD therapy, novel approaches that improve rates of CR/PR and FFS are required that do not cause broad immunosuppression.

References

1. DeFilipp Z. *et al*. Phase I Trial of Brentuximab Vedotin for Steroid-Refractory Chronic Graft-versus-Host Disease after Allogeneic Hematopoietic Cell Transplantation. Biol Blood Marrow Transplant.2018 Sep 24. DOI: 1016/j.bbmt.2018.05.012.