Increasing the levels of anti-beta glucan antibodies by administration of intravenous immunoglobulin (IVIG) induces immunopharmacodynamic (IPD) responses of a novel immunotherapeutic Imprime PGG

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Abstract

Background and Objective: There is a critical need for rational combination immunotherapies that have mechanism-driven predictive biomarkers. Imprime PGG (Imprime), is a novel, intravenously (i.v.) administered innate immunomodulator currently in clinical development as a combination therapy with checkpoint inhibitors in biomarker-selected patients. Imprime is a soluble β-glucan PAMP that requires immune complex formation with serum anti-beta glucan antibodies (ABA) for its functionality. Ex vivo human studies, a healthy volunteer phase I trial and retrospective analyses of clinical studies have demonstrated that IPD changes and clinical responses mediated by Imprime correlated with serum ABA levels. Ex vivo studies have also shown that innate immunity dysfunction in subjects with lower ABA values can be restored by supplementation with purified ABA or ABA-containing IVIG. Herein we present a case study of a cancer patient with low ABA levels demonstrating enhanced Imprime-induced PD responses post IVIG administration.

Methods: A 54-year-old female with metastatic colorectal adenocarcinoma was offered immunotherapy with bevacizumab, cetuximab and Imprime as part of a compassionate use study after she could not tolerate first line therapy with FOLFOX and bevacizumab. The patient was dosed in 4 week cycles for 12 cycles. Imprime and cetuximab were administered i.v. weekly. Bevacizumab was administered every 4 weeks from cycle 2 through 8. Evaluation of serum ABA levels from cycles 1-6 confirmed low values in this patient. To boost ABA levels, IVIG was added to dosing beginning at cycle 6. ABA, complement, and cytokine levels in serum (ELISA and Lumien) were measured with respect to cycles 7 and 8. Increased ABA levels also correlated with significant Imprime binding on neutrophils and monocytes. Importantly, minimal PD changes were observed with Imprime dosing at cycles 1-6 post IVIG administration. Disease remained stable for 10 months.

Results

Healthy Human Volunteer Phase 1: Imprime-Induced IPD Effects Are Restricted to ABA+ Subjects

Healthy Volunteer Phase 1 data:

Biomarkers: [ABA ≥ 20 µg/ml] [PI = 0]

In the Clinic: High ABA Levels Correspond with Better OS in Imprime Treated Patients: Primus 3rd line CRC Trial

Ex vivo:

IVIG addition rescues Imprime binding and function in low ABA subjects

Treatment Schema

Imprime plus IVIG rescues Imprime-driven IPD in a CRC Patient

Conclusions

These human data provide the first evidence of rescue of Imprime-driven IPD responses in a cancer patient by supplementation of ABA, a crucial pre-requisite for the therapeutic activity of Imprime.

• Increased ABA upon IVIG administration
• Increased complement activity
• Enhanced cytokine/chemokine production
• Higher frequency of circulating monocytoid monocytes:
  - Enhanced ADCC potential
  - CDB4HLA-DR

Patient info:

• 54-year-old female with colorectal adenocarcinoma with lymph node metastases.
• 3 cycles of first line chemotherapy with FOLFOX and bevacizumab was not well tolerated, and therefore FOLFOX chemotherapy was stopped and bevacizumab was continued in different intervals for several months. Eventually, tumor started to grow rapidly in metastases in retroperitoneal lymph nodes causing persistent abdominal pain.
• Biothera supported an investigator-initiated study which provided treatment with cetuximab in combination with Imprime every week (1 cycle/4 weeks).
• She had improvement in pain and went off her pain medications. She had fatigue, anorexia rash, diarrhea, hypomagnesemia from her cetuximab therapy.
• Radiographically she appeared to have stable disease.
• After 6 cycles of Imprime, due to her low ABA status, she was co-administered IVIG to boost ABA IgG levels.
• She remained on treatment through cycle 12.