Peripheral Blood Lymphocyte Responses in Patients with Renal Cell Carcinoma Treated with High-Dose Interleukin-2

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BACKGROUND

- Recombinant human interleukin-2 (rhIL-2, aldesleukin) is approved and used for the treatment of metastatic melanoma and renal cell carcinoma.[1-8]
- However, the use of rhIL-2 is limited to patients with normal cardiac and pulmonary function due to associated capillary leak syndrome and resulting hypotension.[9-12]
- Despite the poor tolerability associated with rhIL-2 treatment, it remains one of the few treatment regimens for metastatic melanoma and renal cell carcinoma that elicits a complete and durable response in a subset of patients, up to 12% in melanoma and 7% in renal cell carcinoma.[7,8]
- It has been hypothesized that rhIL-2 preferentially activates and induces the expansion of immunosuppressive $CD4^+$ T_{regs},[13] and high-dose IL-2 is required to induce signaling on receptor complexes expressed on potential tumor killing $CD8^+$ T cells and natural killer (NK) cells.
- Published data show that the immunosuppressive inducible T cell costimulator-positive ($ICOS^+$) T_{regs} were significantly expanded in a subset of melanoma patients receiving high dose IL-2 therapy.[14]
- However, no data are readily available that specifically quantify and compare the levels of expansion of cytotoxic effectors such as $CD8^+$ T cells and NK cells relative to T_{regs}.
- This study was conducted with the primary goal to assess the pharmacodynamic effects of high-dose IL-2 on numbers of circulating $CD8^+$ T cells, NK cells, and T_{regs}.

METHODS

- This was a single-center, open-label study conducted between June 2016 and November 2017.
  - Study center: Beth Israel Deaconess Medical Center, Boston , MA.
  - Study participants: a cohort of patients with renal cell carcinoma receiving treatment with high-dose aldesleukin (IL-2).
- The study was approved by the Beth Israel Deaconess Medical Center IRB, protocol #06-105.
- Aldesleukin at a dose of 600,000 International Units/kg was administered every 8 hours by a 15-min intravenous infusion for a maximum of 14 doses (cycle 1). Following 9 days of rest, the schedule was repeated (cycle 2) for a maximum of 28 doses, as tolerated.
- Whole blood samples for immunophenotyping by flow cytometry were collected at four time points per patient:
  - Cycle 1 prior to the first dose
  - Cycle 1 within 24 hours after the last dose
  - Cycle 2 prior to the first dose
  - Cycle 2 within 24 hours after the last dose
- $CD8^+$ T cells, NK cells, and T_{regs} were quantified by flow cytometry.
- Safety and antitumor activity were monitored throughout the study period.
- Response was assessed clinically based on radiology reports, and best response was recorded.

RESULTS

Baseline Demographic Characteristics

- Ten patients with renal cell carcinoma were enrolled
- Median age 55 (range 39-62)
- Male/female 6/4
- ECOG PS of 0=9/1=1
- Median number of prior therapies 2 (range 1-3)

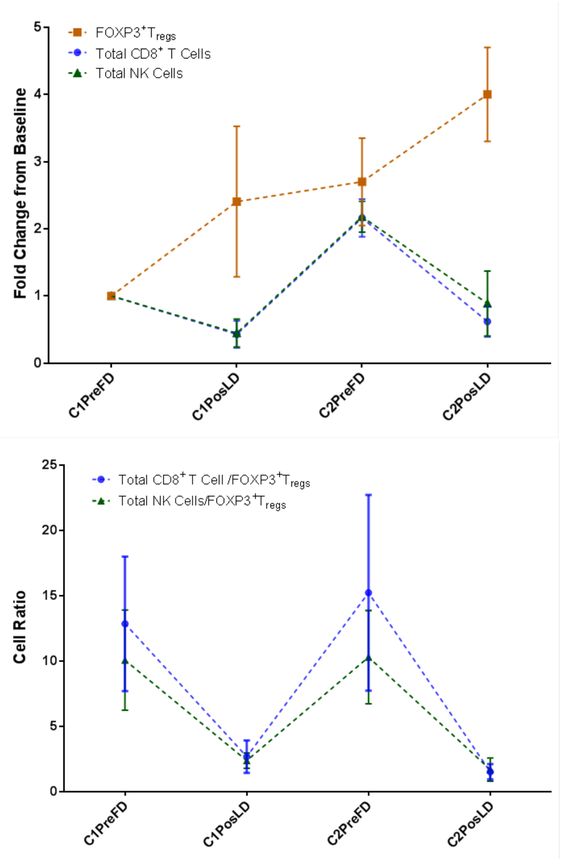
Number of Doses Received

- Cycle 1: median 11 (range 8-13)
- Cycle 2: median 6 (range 0-11)
- Total (cycle 1 + cycle 2): median 17 (range 11-23)

Best Clinical Response

- Partial response (PR): 5
- Mixed response: 1
- Progressive disease (PD): 4

Pharmacodynamic Response



C1PreFD = Cycle 1 prior to the first dose; C1PosLD = Cycle 1 post the last dose; C2PreFD = Cycle 2 prior to the first dose; C2PosLD = Cycle 2 post the last dose.

- Administration of high-dose IL-2 resulted in robust expansion of circulating T_{regs} with a mean maximum expansion of ~4-fold as compared to ~2-fold expansion of circulating total $CD8^+$ T cells and NK cells.
- Minimal or no change to the ratio of NK cells/T_{regs} and $CD8^+$ T cells/T_{regs} was observed in response to high-dose IL-2.
- High inter-subject variability in pharmacodynamic response was observed with no apparent correlation to clinical response and number of doses received.

Treatment-Emergent Adverse Events

Adverse Event	# Patients (%) N = 10
Hypotension requiring vasopressors	8 (80%)*
Elevated bilirubin	7 (70%)
Erythematous rash	7 (70%)
Thrombocytopenia	7 (70%)
Diarrhea	7 (70%)
Nausea	6 (60%)
Acute kidney injury	6 (60%)
Vomiting	5 (50%)
Metabolic acidosis	4 (40%)
Rigors	3 (30%)
Toxic encephalopathy	3 (30%)
Dyspnea	2 (20%)
Neutropenia	1 (10%)
Fatigue	1 (10%)
Leukopenia	1 (10%)
Hyponatremia	1 (10%)
Arthralgias	1 (10%)
Gastrointestinal bleeding (prior nivolumab)	1 (10%)

*Including capillary leak syndrome in 5 patients

- All treatment emergent adverse events seen were consistent with the known adverse event profile of high-dose IL-2.[15]

CONCLUSIONS

- The safety profile and clinical response observed in this small cohort of patients were similar to previously published data.[15]
- A more robust expansion of T_{regs} over $CD8^+$ T cells and NK cells was observed in patients treated with high-dose IL-2, consistent with the known biological activities of IL-2.
- These results may be useful in the future for evaluating possible differences in immune response observed with novel cytokine therapeutic agents.

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DISCLOSURES

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