

Clinical Investigator Training Course (CITC)

Organ Specific Toxicities

Oncology and Immunotherapies

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Disclosures

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Amgen: Global Oncology Advisory Board Member

KinaRx: Co-Founder and Scientific Advisor

Learning Objectives

1. To discuss chemotherapy-induced Myelosuppression & Differentiation Syndrome
2. To explain cytokine release syndrome (CRS) and neurotoxicity related to Bi-specific T-cell engager (BiTE) and Chimeric Antigen Receptor (CAR)-T Cell
3. To learn about immune-related Adverse Events (irAE)

Myelosuppression

- A 75 yo woman presented with WBC 116K/ μ L (90% blast), Hgb 6.2 g/dL, Platelet 53K/ μ L
- Diagnosed with AML, normal cytogenetics, IDH1, NRAS, PTPN11, NF1, NPM1 mutations
- Enrolled in the LLS-sponsored Beat AML trial; Azacitidine + an IDH1 inhibitor
- Hospital course complicated with neutropenic fever, fungal pneumonia
- Remained moderately to severely pancytopenic for 3 cycles (~12-14 weeks)
- **Treatment was not delayed**
- Anti-viral, anti-fungal and anti-bacterial prophylaxis/therapy continued
- No G-CSF was given

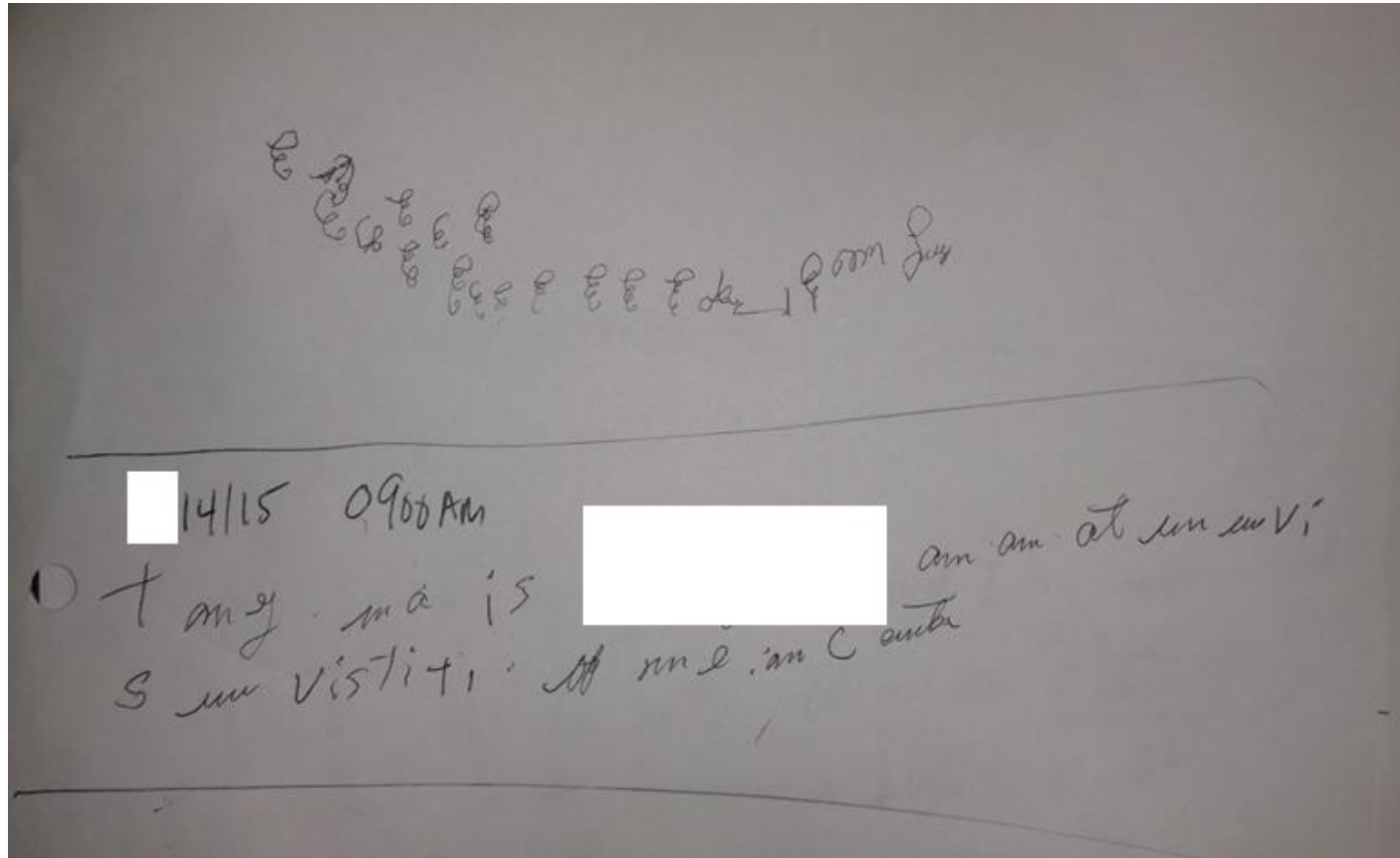
Myelosuppression

- Benefit / Risk Analysis: Curative, Life-Extending, Palliative
- Phases of Clinical Trial
 - (1 [First-In-Human, Define DLT & MTD, Initiate development of adverse event profile], 2, 3)
- General DLT Criteria:
 - \geq Grade 3 non-heme toxicity
 - Grade 4 neutropenia $>$ 7 days
 - Grade 4 thrombocytopenia
 - Bone marrow hypoplasia/aplasia persists $>$ 6-8 weeks
- Differs per cancer type: Hematologic vs. Solid

Differentiation Syndrome

- She was hospitalized on Cycle 1 Day 14 for worsening leukocytosis (WBC 41.7K/ μ L)
- Concerns for relapse versus differentiation syndrome
- Peripheral smear: monocytosis and scattered blasts (4%)
- Treated with hydroxyurea (cytoreduction) and dexamethasone, continued with the experimental agent
- WBC trended down to a nadir of 4.8K/ μ L on the day of discharge
- Achieved complete remission with minimal residual disease negative after two cycles of full dose treatment without interruption
- **Differentiation syndrome (Fever, Weight gain >5 kg, hypotension, dyspnea, lung radiographic opacities, pleural or pericardial effusion or ascites, acute renal failure)**
- **potentially fatal complication of treatment with all-trans retinoic acid (ATRA) and/or arsenic trioxide (As_2O_3), and with inhibitors of isocitrate dehydrogenase (IDH), and FLT3.**

An 54 yo w/ relapsed B-ALL, was started on blinatumomab



- Neuropsychiatric AEs occur in ~50% of patients receiving BiTE or CAR-T, and they may be severe, life-threatening, or fatal
- \geq Grade 3 in ~15% of patients, including encephalopathy, seizures, speech disorders, disturbance of consciousness, confusion, disorientation, and coordination and balance disorders.

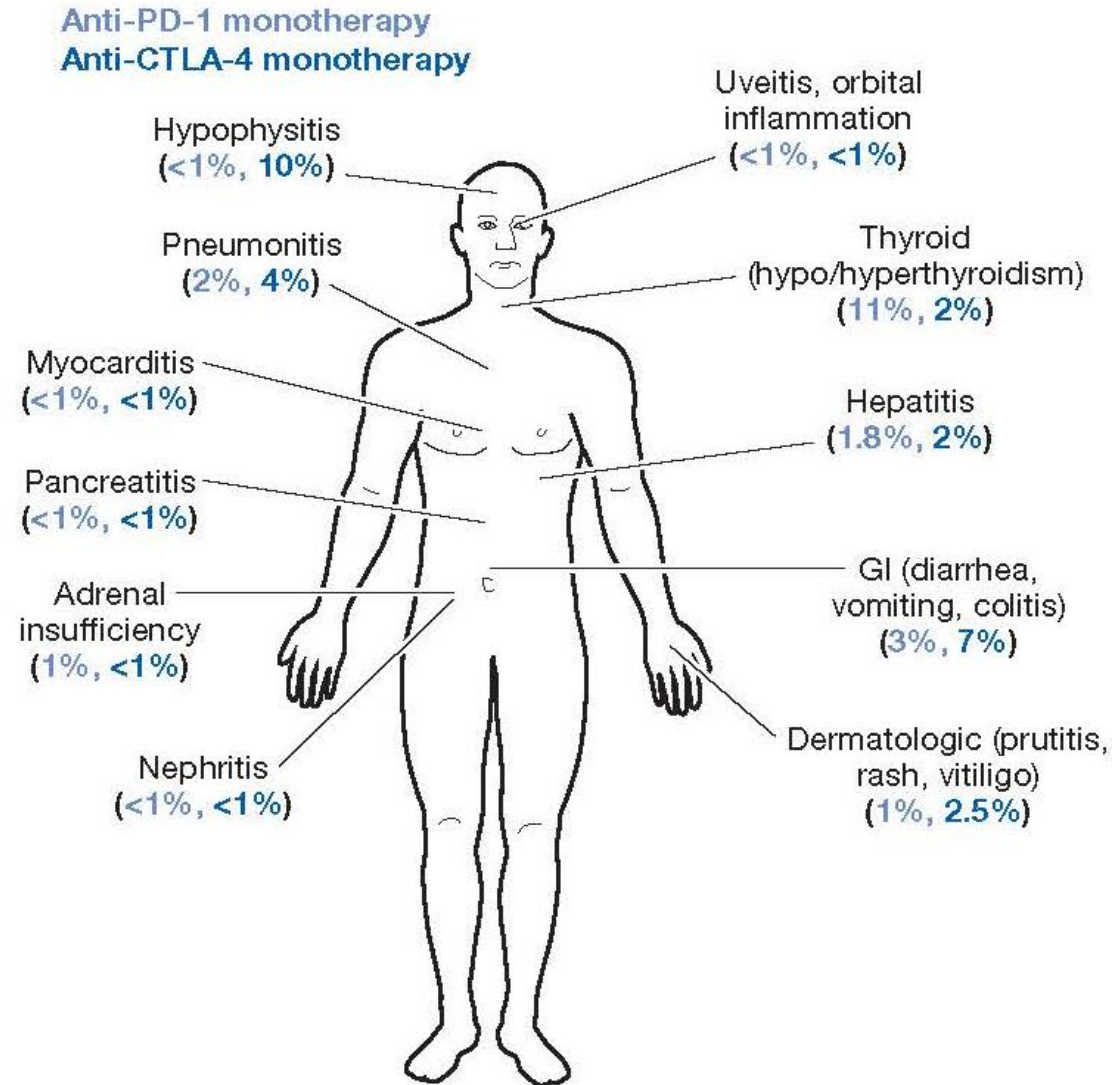
Neurologic complications of BiTE and CAR-T cell Therapy

- 49 y/o man s/p 7 cycles of hyperCVAD, relapsed with Philadelphia Chromosome negative B-ALL, referred for clinical trial with blinatumomab
- Mild cognitive dysfunction, tremors and dizziness on Day 5
- Blinatumomab was continued while closely monitoring patient, symptoms resolved on Day 7
- Dose increased to 28 mcg / day
- Developed moderate speech disturbance and altered mental status and abnormal hand writing on Day 11
- Blinatumomab was held, dexamethasone started 8 mg IV tid, symptoms resolved on Day 13, blinatumomab reinitiated, and was tolerated well
- Achieved CR2 after the first cycle of blinatumomab

- CRS
 - Fever
 - \pm hypotension (responsive to IV fluid or low dose of one vasopressor or multiple vasopressor)
 - \pm hypoxia (O_2 requirement $< 40\%$ or $\geq 40\%$ FiO_2)
 - \pm end-organ dysfunction that develops hours to days after treatment with immune therapy
- DDX:
 - Sepsis
 - Thromboembolism
 - Allergic reaction
 - Hemophagocytic lymphohistiocytosis (HLH)/macrophage activation syndrome (MAS)
 - Tumor progression

- 32 yo man with multiply relapsed B-ALL received CAR-T on August 27th
- Developed high grade fever 8/30th, was given one dose of tocilizumab & started on cefepime
- 36 hours after significant decrease in peripheral blasts, developed high grade fever, hypotension, tachycardia
- cefepime was changed to meropenem and tocilizumab (8 mg/Kg) given for CRS
- Blood culture grew E. Coli

Immune-related adverse events (irAEs) after checkpoint inhibitors



- The irAEs resemble and are treated similarly to GVHD in allogeneic HSCT
- Prophylaxis against irAEs is not currently recommended
- Does immunosuppression to treat irAEs reduce antitumor efficacy of treatment of ICIs?
- The frequency, but not the type or quality of irAEs, may increase with dose and may vary among different cancers
- Neither the occurrence of irAEs (irrespective of the grade) nor the use of systemic corticosteroids to treat irAEs affected OS or time to failure in patients treated with immune checkpoint inhibitors

Challenge Question

- 1) TY tolerates the first two weeks of treatment with ATRA and arsenic trioxide for her APL. She was doing well with normal mental status, resolving of diplopia, and no bleeding. On day 15, the patient becomes hypoxic and develops fever. Chest CT demonstrates pulmonary infiltrates and a right-sided pleural effusion and mild pericardial effusion. She is transferred to ICU. What is the most likely diagnosis?
1. Pneumonia and associated parapneumonic effusion.
 2. Extramedullary leukemia
 3. Transfusion related acute lung injury (TRALI)
 4. Differentiation Syndrome
 5. Pulmonary edema due to volume overload

In APL treated with ATRA and/or arsenic trioxide (ATO) or in AML with IDH mutation treated with enasidenib or ivosidenib, the presence of ≥ 3 events is sufficient for a confident clinical diagnosis of differentiation syndrome and should prompt the use of dexamethasone or other steroids. These symptoms/signs include fever $\geq 38^{\circ}$ C, weight gain >5 kg, hypotension, dyspnea, radiographic opacities, pleural or pericardial effusion, acute renal failure

Challenge Question

- **Patients with history of autoimmune disorders are generally excluded from trials involving immune checkpoint inhibitors (ICI). What is the evidence for this?**
- Retrospective cohort study (Jan 2017 - Jan 2018) via 3 national networks of experts in oncology and autoimmunity in France.
- N=112, median follow up = 8 months, most frequent Preexisting Autoimmune Diseases (PAD) were psoriasis (n=31), rheumatoid arthritis (n=20) and inflammatory bowel disease (n=14).
- PAD flare and/or other irAE(s) occurred in 79 pts (71%), including PAD flare in 53 pts (47%) and/or other irAE(s) in 47 pts (42%), with the need of immunosuppressive therapy for 48 pts (43%) and ICI permanent discontinuation for 24 pts (21%).
- Median PFS was shorter in pts receiving immunosuppressive therapy at ICI initiation (3.8 versus 12 months; $p= 0.006$), confirmed with multivariable analysis.
- **CONCLUSION:** The occurrence of a flare/irAE is frequent but mostly manageable without ICI discontinuation in pts with PAD. Immunosuppressive therapy at baseline was associated with poorer outcomes.