Atezolizumab

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Continuing Education Activity

Atezolizumab is a humanized IgG1 monoclonal anti-programmed death-ligand 1 (PD-L1) antibody that has been approved by the U.S Food Drug Administration (FDA) for various neoplastic conditions either as a single agent or in combination with other chemotherapeutic agents. Atezolizumab is a drug that is used in the management and treatment of various neoplastic conditions. It is in the monoclonal antibody class of medications. This activity covers the indications, contraindications, adverse events, and other therapeutic factors clinicians need to know to drive patient outcomes effectively.

Objectives:

- Summarize mechanism of action of atezolizumab.
- Describe the adverse effects of atezolizumab.
- Review the pharmacokinetics and monitoring for immune-mediated adverse reactions related to atezolizumab.
- Outline the importance of an interprofessional team approach and care coordination when treating patients with atezolizumab.

Access free multiple choice questions on this topic.

Indications

Atezolizumab is a humanized IgG1 monoclonal anti-programmed death-ligand 1 (PD-L1) antibody that has been approved by the U.S Food Drug Administration (FDA) for various neoplastic conditions either as a single agent or in combination with other chemotherapeutic agents. Atezolizumab is FDA approved for the following neoplastic conditions:[1]

Locally Advanced or Metastatic Urothelial Carcinoma

- **Atezolizumab, as a single agent, is indicated in patients with locally advanced or metastatic urothelial carcinoma.**
    - Who are ineligible for cisplatin-containing chemotherapy with a level of tumor PD-L1 expression, or
    - Are ineligible for any platinum-containing chemotherapy irrespective of their PD-L1expression status, or
    - Have the progression of their disease during or following any platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant chemotherapy[2][3][2]
- **Extensive-stage Small Cell Lung Cancer**
    - Atezolizumab, in combination with carboplatin and etoposide, is indicated as the first-line treatment of adult patients with extensive-stage small-cell lung cancer.[4]
- **Metastatic Non-small-cell Lung Cancer (NSCLC)**
    - Atezolizumab, as a single agent, is indicated in patients with metastatic NSCLC with high PD-L1 expression, regardless of histologic type.
    - Atezolizumab, in combination with bevacizumab plus chemotherapy (paclitaxel and carboplatin), is indicated for the first-line treatment of adult patients with metastatic non-squamous NSCLC regardless of PD-L1 expression and (epidermal growth factor receptor)EGFR or anaplastic lymphoma kinase (ALK) genomic tumor alterations.
    - Atezolizumab in combination with nanoparticle albumin-bound paclitaxel and carboplatin is indicated for the first-line treatment of adult patients with metastatic non-squamous NSCLC with no EGFR or ALK genomic tumor aberrations.
    - Atezolizumab as a single agent is indicated for treating adult patients with metastatic NSCLC who have disease progression during or despite receiving platinum-containing chemotherapy.[4][5]
- **Metastatic Triple-negative Breast Cancer**
    - Atezolizumab, in combination with nanoparticle albumin-bound paclitaxel, is indicated for the treatment of adult patients with unresectable locally advanced or metastatic triple-negative breast cancer whose tumors express PD-L1.[6]

Unresectable or Metastatic Hepatocellular Carcinoma

- Atezolizumab, in combination with bevacizumab, is indicated to treat patients with unresectable or metastatic hepatocellular carcinoma (HCC) who have not previously received treatment with chemotherapy.[7]

Unresectable or Metastatic Melanoma

- Atezolizumab, in combination with vemurafenib and cobimetinib, is indicated to treat patients with BRAF mutation-positive unresectable or metastatic melanoma.[8]

Mechanism of Action

Many immune and tumor-infiltrating cells express programmed death-ligand 1 (PD-L1), that negatively regulates the cytotoxic T-lymphocyte activation by binding to the programmed death-1 (PD-1) and B7.1 (CD80) receptors that cause suppression of T-cell migration, proliferation, and secretion of cytotoxic mediators leading to inhibited tumor cell killing.[9]

Data from many clinical trials have shown that agents targeted at the PD-L1/PD-1 molecular pathway can induce antitumor activity early and across multiple neoplastic conditions. Atezolizumab is a humanized monoclonal anti-programmed death-ligand 1 (PD-L1) antibody that inhibits PD-L1–programmed death 1 (PD-1) PD-L1–B7-1 signaling, thereby resulting in tumor-specific cytotoxic T-cell immunity.[10]

Administration

Atezolizumab is FDA-approved for intravenous use only. It is available in two different concentrated strength solutions of 840 mg/14 mL (60 mg/mL) and 1200 mg/20 mL (60 mg/mL) in a single-dose vial. Atezolizumab is recommended to be administered as an IV infusion after dilution with 0.9 % sodium chloride injection. The infusion's initial rate should be over 60 minutes, and if well tolerated, subsequent doses can be administered over 30 minutes. Patients should be closely monitored for infusion-related reactions, based on the severity of which the infusion rate must be interrupted temporarily, or the infusion rate must be slowed or permanently discontinued.

Dosing is generally 1200 mg IV every three weeks for most indicated cancers (unresectable or metastatic melanoma dosing is 840 mg IV every two weeks); depending on the diagnosis and institution, dosing can vary from this standard regiment. The clinician should always consult the drug package insert and institutional protocols before designing a dosing regimen for any patient.

Adverse Effects

As with other approved PD-1/PD-L1-targeted therapies, the use of atezolizumab can be associated with immune-mediated adverse events (imAEs), which can be severe or fatal and involve any organ system manifesting as described below.[11][12][13]

Infusion-related Reactions

- Anaphylaxis and hypersensitivity

Immune-mediated Colitis

- Immune-mediated colitis is characterized by signs and symptoms of diarrhea or increased ostomy output, colitis, and or perforation. All other etiologies of diarrhea and colitis should be excluded, including endoscopic evaluation. Based on the clinical and endoscopic severity, immune-mediated colitis is classified into four different grades:
    - **Grade 1**: < 4 stools per day or mild increase in ostomy output compared to baseline
    - **Grade 2**: 4 to 6 stools per day or moderate increase in ostomy output compared to baseline (compared with baseline) and/or colitis symptoms
    - **Grade 3**: ≥7 stools per day or severe increase in ostomy output compared to baseline with colitis
    - **Grade 4**: Severe colitis resulting in bowel perforation requiring urgent surgical intervention

Immune-mediated Cutaneous Adverse Effects

- Immune-mediated cutaneous adverse reactions are common and manifest as itching, maculopapular rash, lichenoid reactions, vitiligo, and pruritus.
- Based on the clinical severity and percentage of involvement of the body surface area, they are classified into four grades:
    - **Grade 1**: asymptomatic with macules/papules involving <10% of the body surface area
    - **Grade 2**: macules/papules involving 10% to 30% of the body surface area with or without symptoms

- **Grade 3**: macules/papules involving >30% of the body surface area with or without symptoms
- **Grade 4**: Severe cutaneous reactions such as Stevens-Johnson syndrome, TEN, and bullous dermatitis covering >30% of BSA and requiring intensive care unit (ICU) admission.

Immune-mediated Endocrinopathies

- Immune-mediated endocrinopathies can present with signs and symptoms of adrenal insufficiency, thyroiditis, hypothyroidism, hyperthyroidism, hypophysitis, and diabetes, either alone related to one endocrine organ or in combination.

Immune-mediated Hepatitis

- Immune-Mediated Hepatitis typically manifests with elevation in liver function tests.
- Based on the severity of liver test abnormalities and hepatic dysfunction, immune-mediated hepatitis is classified into four types:

  - **Grade 1**: Elevation of AST/ALT < 3 times the upper limit of normal(ULN) and/or total bilirubin <1.5 times ULN
  - **Grade 2**: Elevation of AST/ALT 3 to 5 times ULN and/or total bilirubin >1.5 to ≤ 3 times ULN
  - **Grade 3**: Elevation of AST/ALT AST/ALT > 5 to 20 times ULN and/or total bilirubin 3–10x ULN
  - **Grade 4**: AST/ALT > 20x ULN, and/or total bilirubin >10x ULN associated with signs and symptoms of liver dysfunction.

Immune-mediated Pneumonitis or Interstitial Lung Disease

- Immune-Mediated pneumonitis is characterized by nonproductive cough, shortness of breath, and radiological abnormalities of the lung.
- Based on clinical severity and radiological involvement, immune-mediated pneumonitis is classified into four different types:

  - **Grade 1**: asymptomatic and limited to <25% involvement of the lung parenchyma or one lobe of the lung
  - **Grade 2**: moderate symptoms and involvement of 25 to 50% of the lung parenchyma or more than one lobe of the lung
  - **Grade 3**: severe symptoms and involvement of >50% of the lung parenchyma or all lung lobes
  - **Grade 4**: acute respiratory distress requiring mechanical ventilation.

Immune-mediated Renal Dysfunction and Nephritis

- Immune-mediated renal dysfunction typically manifests with increased creatinine levels and is graded into four types of severity based on the renal function:

  - **Grade 1**: An increase in creatinine level >0.3 mg/dL or 1.5 to 2.0 times compared to a baseline value
  - **Grade 2**: An increase in creatinine level 2 to 3 times compared to a baseline value
  - **Grade 3**: An increase in creatinine level >4.0 mg/dL or >3 times compared to a baseline value
  - **Grade 4**: Worsening renal function requiring hemodialysis)

Immune-mediated Neurological Toxicities

The incidence of immune-mediated neurological toxicity is 1 % and is characterized by clinical symptoms of polyneuropathy, facial nerve palsy, aseptic meningitis, transverse myelitis, myasthenia gravis, Guillain Barre syndrome(GBS), or posterior reversible leukoencephalopathy.

Other common adverse reactions that occurred with atezolizumab as a single agent in clinical trials participants include:[14][4]

- Musculoskeletal (back pain, neck pain)
- Metabolism (decreased appetite, hyperglycemia, hyponatremia, hyperkalemia, hypermagnesemia, hypophosphatemia)
- Dermatologic (pruritus, rash)
- Respiratory (cough, dyspnea)
- General (fatigue, pyrexia, asthenia)
- Gastrointestinal (abdominal pain, diarrhea, constipation, nausea)
- Endocrine (hypothyroidism)
- Infectious (pneumonia, urinary tract infection)
- Blood/lymphatic (anemia, thrombocytopenia, lymphopenia)
- Hepatobiliary (elevated liver function tests)
- Renal (increase serum creatinine)

Monitoring

Patients receiving atezolizumab are at risk of developing immune-mediated adverse reactions anytime during therapy and after treatment discontinuation. Early identification and management of imAEs are crucial in patients receiving atezolizumab.[15]

- Patients should be monitored for signs and symptoms of exfoliative dermatological manifestations, autoimmune colitis, endocrinopathies, immune-mediated neurological and cardiovascular involvement.
- Laboratory tests such as blood glucose level, renal function, liver function, and thyroid function should be performed at baseline before initiation of treatment and during treatment to evaluate for new-onset diabetes, adverse reactions such as immune-mediated nephritis, immune-mediated hepatitis, and immune-mediated thyroid dysfunction, respectively.
- Atezolizumab must be held in Grade 2 immune-mediated adverse reactions and should be permanently discontinued in Grade 3 and Grade 4 immune-mediated adverse reactions unless indicated by the oncology team.

Toxicity

There is no available data regarding the safety of atezolizumab in pediatric patients and pregnant or breastfeeding women.[12][11] There is also no available data about the drug-drug interaction potential of atezolizumab.[13]

Immune-Mediated Colitis

- Grade 1 colitis should be treated with symptomatic management.
- Atezolizumab must be held in Grade 2 and Grade 3 colitis, and patients should be started on steroids with a slow taper.
- Atezolizumab should be permanently discontinued in Grade 4 colitis.

Immune-Mediated Pneumonitis

- Tapering corticosteroids is recommended if there is evidence of pneumonitis or interstitial lung disease on lung imaging.
- Atezolizumab should be held for Grade 2 pneumonitis and permanently discontinued if there is evidence of Grade 3 or 4 pneumonitis.

Immune-Mediated Hepatitis

- After ruling out viral hepatitis and other etiologies of elevated liver function tests, atezolizumab must be held in Grade 2 hepatitis. Patients should be started on oral or IV steroids followed by a slow taper.
- Atezolizumab must be permanently discontinued in Grade 3 and 4 immune mediated-hepatitis, and patients should be started on IV steroids.

Immune-Mediated Endocrinopathies

- **Thyroid Disorders**
    - If clinically indicated, consider thyroid hormone replacement therapy in hypothyroidism or medical management of hyperthyroidism.
- **Adrenal Insufficiency/Hypophysitis**
    - Consider initiating stress dose corticosteroids and hormone replacement therapy as clinically indicated.
- **Type 1 Diabetes Mellitus**
    - Consider starting insulin if indicated.
- **Atezolizumab should be held in Grades 2 to 4 endocrinopathies.**
- **Immune-mediated Renal Dysfunction and Nephritis**
    - Atezolizumab should be held with grade ≥2 toxicities, and corticosteroid administration should be considered.
- **Immune-mediated Cutaneous Adverse Reactions**
    - Topical steroids are indicated for Grade 1/Grade 2 toxicity.
    - Atezolizumab must be held in Grade 2 and Grade 3 toxicity; patients with Grade 2 toxicity should be treated with PO steroids.
    - Atezolizumab must be permanently discontinued in patients with Grade 4 immune toxicity, and patients should be treated with IV steroids in an intensive care unit(ICU)

Enhancing Healthcare Team Outcomes

Given its propensity to cause immune-mediated adverse reactions, the clinical use of atezolizumab requires an interprofessional team approach of healthcare professionals, including clinicians, nurses, and pharmacists. Clinicians prescribing this drug should educate their patients about the immediate and long-term adverse reactions. The clinical pharmacist should educate the nurse administering the drug infusion to the patients about the mechanism of action, recommended doses, and infusion-related adverse reactions of atezolizumab. Laboratory tests must be performed and reviewed before and during treatment with atezolizumab. This interprofessional approach will yield optimal therapeutic results. [Level 5]

There should be close communication between the ordering physician, the pharmacist, and the nurse about any infusion-related reactions or laboratory abnormalities related to the drug. Signs and symptoms of immune-mediated adverse reactions during treatment or long after discontinuation of atezolizumab should be monitored, and appropriate clinical investigations must be performed to rule out other etiologies. Detailed prescribing information for important dose management information specific to adverse reactions should be available for review at all times. Applicable clinical specialties must be promptly consulted. Such a holistic approach would lead to timely identification and management of this drug's potential side effects, resulting in improved outcomes.

Review Questions

- Access free multiple choice questions on this topic.
- Comment on this article.

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