MultipleMyelomaHub

Relapsed/refractory patients

Selinexor for refractory myeloma

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Ajai Chari from Mount Sinai Hospital, New York, US and colleagues conducted a multicenter, open-label, single arm, phase IIb trial to determine the efficacy and safety of treatment with selinexor and dexamethasone for triple-class refractory myeloma.[1] This formed part two of the STORM study (which the Multiple Myeloma Hub has previously discussed alongside associated studies here and here).

Exportin 1 (XPO1) is involved in the exportation of nuclear proteins such as tumor suppressor proteins. XPO1 has been found to be over-expressed in multiple myeloma cells and correlates with decreased survival.[1] Selinexor, which recently achieved Food and Drug Administration (FDA) approval,[2] is an inhibitor of XPO1 and has been found to induce apoptosis in myeloma cell lines and animal models.[1]

The STORM study administered 80 mg selinexor alongside 20 mg dexamethasone on days 1 and 3 of every week for 4-week cycles to assess safety (n=123) and efficacy (n=122).

Findings:

- Patients
  - Median age was 65.2 years
  - Median duration of myeloma was 6.6 years
  - 53% of patients had high-risk cytogenetic mutations
  - Median number of previous therapies was 7 (range 3–18)
- Treatment
  - 118 (96%) patients discontinued treatment, with disease progression or adverse events the most common causes
  - At last follow-up, five (4%) continued treatment, and 34 (28%) had discontinued treatment but remained in follow-up for long-term survival
  - Median duration of treatment was 9.0 weeks (range 1–60)
- Efficacy
  - Overall response rate: 26.0% (95% CI, 19.0–35.0)
    - Two complete responses (CR), six very good partial responses (VGPR), and 24 partial responses (PR)
  - Median time to PR or better was 4.1 weeks (range 1–14)
  - Median duration of response in responders (n=32): 4.4 months (95% CI, 3.7–10.8)
  - Patients who had a response (minimal/partial/complete) had median overall survival of 15.6 months

- Safety (n=123)
  - Mortality during study: n=28
  - Causes of mortality: disease progression (n=16), adverse events (n=12)
    - Two of these fatal adverse events were assessed as being related to treatment (pneumonia with disease progression, and sepsis)
  - Most common grade 3 or 4 adverse events were thrombocytopenia (59% of patients), anemia (44%), fatigue (25%), hyponatremia (22%) and neutropenia (21%)
  - Treatment-emergent adverse event (TEAE) of any grade: 100%
  - 18% of patients discontinued study treatment due to a TEAE
- Selinexor response biomarkers
  - Pre-treatment blood samples, which included 16 responders and 19 non-responders, identified a four-protein classifier (IRF3, ARL2BP, ZBTB17, and ATRX) which had a prediction accuracy of 83% (95% CI, 55–95)

Conclusion

Chari and colleagues concluded that selinexor (oral) alongside dexamethasone induced a response in just over a quarter of patients who had received many different therapeutic regimens but still had refractory myeloma. The most common toxic effects that were graded as 3 or above included thrombocytopenia without bleeding, anemia, neutropenia without fever, and hyponatremia. Thrombocytopenia, due in part to inhibition of thrombopoietin signaling in early megakaryopoiesis, was reversible and managed by dose interruption and thrombopoietin-receptor agonists. Selinexor preclinical studies show enhancement of IκB, which supports possible future use in combination with proteasome inhibitors, immunomodulatory drugs, and/or sensitization of myeloma cells to anti-CD38 monoclonal antibodies.

References

1. Chari A. et al. Oral selinexor–dexamethasone for triple-class refractory multiple myeloma. *N Engl J Med*. 2019 Aug 22; 381(8):727–738. DOI: 10.1056/NEJMoa1903455
2. U.S. Food and Drug Administration. FDA grants accelerated approval to selinexor for multiple myeloma: https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-selinexor-multiple-myeloma [accessed Sept 12 2019]