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HL

Brentuximab vedotin, dexamethasone, high-dose cytarabine, and cisplatin for R/R cHL

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In a recent issue of *Haematologica*, Anton Hagenbeek from the University of Amsterdam, NL, and colleagues, published the results of the multicentre, phase I, Transplant BraVE trial (NCT02280993). In this dose-escalation study, the combination of brentuximab vedotin (BV) with dexamethasone, high-dose cytarabine, and cisplatin (DHAP) was assessed as salvage treatment in relapsed/refractory (R/R) classical Hodgkin lymphoma (cHL).

The combination of BV with chemotherapy can be associated with significant toxicity, overweighing any potential tumor reduction benefits. Nevertheless, DHAP alone has been associated with both a tolerable profile and promising clinical responses in R/R cHL patients. The aim of this phase I trial was to evaluate the feasibility of combining BV and DHAP treatment in R/R cHL patients and to establish the recommended dose level (RDL). Secondary endpoints included safety, metabolic response rate assessed by fluorodeoxyglucose-positron emission tomography/computed tomography (FDG-PET/CT), and success of autologous peripheral blood stem cell harvest after treatment.

Study design

- N = 12 eligible patients with histologically confirmed CD30-positive R/R cHL
- Median age (range): 30.5 (21–56) years
- Dosing of BV-DHAP (three 21-day long cycles):
  - BV: 1.8 mg/kg on Day 1 of each DHAP cycle with escalation of cisplatin and cytarabine. BV was combined with either a) 75% of the cisplatin dose on Day 1 and 75% of cytarabine on Day 2 (dose level 1); b) 75% cisplatin and 100% cytarabine (DL 2); or c) full dose of all agents (DL 3)
  - DL1: n = 3 patients; DL2: n = 3 patients, and DL3: n = 6 patients
  - DHAP:
    - Dexamethasone (40 mg between Days 1–4)
    - Cisplatin (full dose: 100 mg/m^2)
    - Cytarabine (full dose: 2 g/m^2 every 12 hours; two doses)
  - For stem cell mobilization, 5 µg/kg of granulocyte-colony stimulating factor (G-CSF) was administered twice daily from Day 10 of BV-DHAP cycle 2 until stem cell harvest
- Dose escalation was stopped if at least two patients experience a dose limiting toxicity (DLT) or when the highest planned dose level was reached
- Following BV-DHAP, patients continued with BEAM (carmustine [300 mg/m^2]; cytarabine [200 mg/m^2]; etoposide [200 mg/m^2]; melaphalan [140 mg/m^2]) within 28 and no later than 42 days after the initiation of the third BV-DHAP cycle

- Median time from primary diagnosis to the first BV-DHAP cycle (range): 1.2 (0.7–11.2) years

Results

- Metabolic complete response (CMR) was observed in 92% of patients (n = 11/12)
- Stem cell harvest was successful in all patients after one round of stem cell apheresis (median yield (range): 5.3 x 10^6 (3.0–25.9) $CD34^+$ cells/kg)
- Following BEAM and autologous stem cell transplant (ASCT):
  - Median time to absolute neutrophil count (ANC) recovery (range) was 14.5 (8–43) days
  - 92% of patients (n = 11/12) were in CMR and one patient had a biopsy-proven CR
  - After a median follow-up (range): 2.0 (1.8–3.0) years, all patients remained alive and in CR

Safety

- Grade 3–4 adverse events (AEs) were reported in n = 7 patients:
  - Neutropenia (Grade 4; n = 2; DL1)
  - Neutropenia (Grade 3; n = 1; DL3)
  - Thrombocytopenia (Grade 4; n = 1; DL3)
  - Thromboembolic event (Grade 3; n = 1; DL1)
  - Elevated transaminases (Grade 3; n = 1; DL3)
  - Leukocytosis (Grade 4; n = 1; DL3)
  - Hypokalemia (n = 1; DL3)
- No motor peripheral neuropathy (PNP) was observed
- Ten serious AEs were reported in n = 4 patients (30%) all at DL3. The majority of these were not believed to be treatment-related (except for one case of atrial fibrillation and acute liver failure in the same patient)

These preliminary results of the Transplant BraVE phase I trial indicate that the combination of BV and DHAP is feasible in R/R cHL patients, even at the maximum dose tested. The treatment also presented an acceptable toxicity profile and good response rates, paving the way for the ongoing phase II study on BV-DHAP at DL3 in sixty R/R cHL patients (NCT02280993).

References

1. Hagenbeek A. *et al.* Phase 1 dose-escalation study of brentuximab-vedotin combined with dexamethasone, high-dose cytarabine and cisplatin, as salvage treatment in relapsed/refractory classical Hodgkin lymphoma: the Transplant BRaVE study. *Haematologica*. 2018 Oct 31. pii: haematol.2018.196899. DOI: 10.3324/haematol.2018.196899 [Epub ahead of print].

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