A new paradigm shift in frontline treatment of Hodgkin lymphoma

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Background: Hodgkin lymphoma (HL) is one of the success stories of modern oncology, with more than 90% of patients alive and 80% considered cured after long-term follow-up. Improved outcome is the result of numerous factors including more accurate staging, more effective chemo and chemo-radiotherapy, and newer targeted agents. More recently risk-adapted strategies using PET-CT have further enhanced outcomes for high-risk patients, while reducing toxicities for low risk patients. In advanced-stage disease, even after a PET adapted strategy, approximately 15-20% of patients fail primary treatment for primary chemo-refractoriness or relapse following frontline ABVD treatment. Brentuximab vedotin is a CD30-directed antibody-drug conjugate approved for classical HL after failure of autologous stem cell transplantation (ASCT) or ≥2 prior chemotherapy regimens and as consolidation post-ASCT for increased risk HL.

Echelon-1 Trial In 2012, a open-label, randomized, multicenter, phase 3 study, the Echelon-1 trial, was launched to compare the effectiveness, in terms of 2-y modified PFS (mPFS), of AVD plus Brentuximab-Vedotin (A+AVD) versus standard ABVD as frontline therapy in previously untreated stage III and IV HL in 218 oncology/Hematology institutions all over the world (Echelon-1 trial).

Thirteen-hundred-thirty-four Stage III (36%) or IV (64%) HL patients were randomized (58% male; median age 36 y [range 18-83]; ≥45 y, 34%; ≥60 y, 14%). The primary endpoint of modified PFS (mPFS) per IRF was met (HR 0.770 [95% CI 0.603-0.982]; p=0.035), with 117 events in the A+AVD arm and 146 events in the ABVD arm, and was consistent with investigator (INV)-reported modified PFS (HR 0.725 [95% CI 0.574-0.916]; p=0.007). Modified PFS events per IRF were attributed to disease progression (90 vs 102); death (18 vs 22) or receipt of additional anticancer therapy for incomplete response (9 vs 22) after A+AVD or ABVD, respectively. The 2-y mPFS per IRF was 82.1% (95% CI 78.7-85.0) with A+AVD vs 77.2% (95% CI 73.7-80.4) with ABVD. Pre-specified subgroup analysis of mPFS per IRF demonstrated a consistent benefit of the experimental treatment over standard ABVD in patients with stage IV and ≥1 extranodal site. A subset analysis on 186 elderly patients (≥ 60) enrolled in Echelon-1 trial, accounting for 14% of the entire enrolled population, showed no difference in terms of 2-Y mPFS per IRF of the experimental arm over the standard arm in the overall elderly population and only a slight, non-significant benefit for stage iv patients (2-Y mPFS: 71.3 Vs. 66 1%; p= 0.5069. after a mean follow-up of 30 months 15 patients in A+AVD, 8 of them with stage IV and 17 patients in ABVD arm, 13 of them with stage IV had an event. 66/83 patients in the experimental arm and 70/98 in the standard arm had dose modification of treatment and the most frequent dose modification were due to BV (mean 92.35% DI) or Bleomycin (mean 88.7% DI) dose reduction, respectively. The emergence of grade ≥3 AEs were higher in elderly compared to younger patients, febrile neutropenia (FN) and pulmonary toxicity being the most frequents SAEs in experimental and standard treatment, respectively. G-CSF prophylaxis was able to reduce significantly the in cadence of FN in the experimental arm.

Conclusions: the Echelon-1 trial showed a significantly superior modified PFS of A-AVD over ABVD per Independent review, with a 23% reduction in risk of progression, death or need for additional anticancer therapy, and a 2-year modified PFS of 82% Vs. 77% of the standard ABVD arm. These results will be compared with those obtained in the recently published PET-adapted clinical trials in advanced HL.