Endobronchial Valves for Severe Emphysema

Kemp SV, Slebos DJ, Kirk A, et al; for the TRANSFORM Study Team. A multicenter randomized controlled trial of Zephyr endobronchial valve treatment in heterogeneous emphysema (TRANSFORM). Am J Respir Crit Care Med 2017;196:1535–43.

Study Overview

Objective. To evaluate the efficacy and safety of Zephyr endobronchial valves (EBVs) in patients with heterogeneous emphysema and absence of collateral ventilation.

Design. Multicenter, randomized, nonblinded clinical trial.

Setting and participants. This study was conducted at 17 sites across Europe between 2014 and 2016. Patients with severe emphysema who were ex-smokers and ≥ 40 years old were recruited. Key inclusion criteria were post-bronchodilator FEV1 between 15%–45% predicted despite optimal medical management, total lung capacity greater than 100% predicted, residual volume ≥ 180% predicted, and a 6-minute walk distance of between 150 and 450 meters. Heterogenous emphysema was defined as a greater than 10% difference in destruction score between target and ipsilateral lobes as measured by high-resolution CT. All eligible patients underwent Chartis pulmonary assessment (Pulmonx, Redwood City, CA) assessment to determine the presence of collateral ventilation between the target and adjacent lobes, and patients with collateral ventilation were excluded.

Intervention. Patients were randomized 2:1 to either EBV plus standard of care (intervention) or standard of care alone (control) by blocked design and concealed envelopes. The EBV group underwent immediate placement of Zephyr EBVs with the intention of complete lobar occlusion.

Main outcome measures. The primary outcome at 3 months post-procedure was the percentage of subjects with FEV1 improvement from baseline of 12% or greater. Changes in FEV1, residual volume, 6-minute walk distance, St. George's Respiratory Questionnaire score and modified Medical Research Council score were assessed at 3 and 6 months and target lobe volume reduction on chest CT at 3 months.

Main results. 97 subjects were randomized to the intervention (n = 65) or control group (n = 32). At 3 months, 55.4% of intervention and 6.5% of control subjects had an FEV1 improvement of 12% or more ($P < 0.001$). Improvements were maintained at 6 months: intervention, 56.3%, versus control, 3.2% ($P < 0.001$), with a mean ± SD change in FEV1% at 6 months of 20.7 ± 29.6% and –8.6 ± 13.0%, respectively. A total of 89.8% of intervention subjects had target lobe volume reduction greater than or equal to 350 mL (mean, 1.09 ± 0.62 L; $P < 0.001$). The differences in outcomes between the intervention and control groups were statistically significant, with the

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following measured differences: residual volume, –700 m; 6-minute walk distance, +78.7 m; St. George's Respiratory Questionnaire score, –6.5 points; modified Medical Research Council dyspnea score, –0.6 points; and BODE (body mass index, airflow obstruction, dyspnea, and exercise capacity) index, –1.8 points (all $P < 0.05$). Pneumothorax was the most common adverse event, occurring in 19 of 65 (29.2%) of intervention subjects.

Conclusion. Endobronchial valve treatment in hyperinflated patients with heterogeneous emphysema without collateral ventilation resulted in clinically meaningful benefits in lung function, dyspnea, exercise tolerance and quality of life, with an acceptable safety profile.

Commentary

Patients with severe emphysema are difficult to manage. Optimal medical management is required to maintain their lung function and quality of life, with combination bronchodilators (long-acting beta 2 agonists, long-acting anticholinergics, and inhaled corticosteroids), roflumilast (selective phosphodiesterase-4 inhibitors), oral corticosteroids or macrolide antibiotics when indicated, long-term oxygen, and noninvasive ventilator support. Palliative team care consultation and support, adequate nutritional support, influenza and pneumococcal vaccination, and pulmonary rehabilitation/graded exercise training are important aspects of emphysema treatment [1].

To help patients with severe emphysema who experience further decline despite intensive medical management, a lung volume reduction strategy was devised. In 2003, the NETT trial was conducted [2]. In this study, lung volume reduction surgery was performed in 608 patients, who were followed for 29 months. This study revealed a lack of survival benefit with significant immediate postoperative mortality and complication rate. Despite this disappointing result, a subgroup of patients (upper-lobe predominant disease and low baseline exercise capacity) had a statistically significant mortality benefit from surgery.

Since then, many have sought to determine a less invasive method of lung volume reduction. So far, one-way endobronchial valves, self-activating coils, and targeted destruction and remodeling of emphysematous lung with vapor or sealant methods have been studied. Several studies have examined the efficacy and safety of coils, with reasonable improvement of 6-minute walk distance and FEV1; however, complications including death, pneumothorax and pneumonia were noted. Vapor ablation (STEP-UP trial) [3] and lung sealant [4] were also attempted in order to achieve lung volume reduction, but increased infection was problematic. The 2017 GOLD guidelines suggested lung volume reduction by endobronchial one-way valve or lung coils as interventional bronchoscopic options for lung volume reduction [1].

Two types of endobronchial valves have been introduced to date: the intra bronchial valve, developed by Olympus, and the Zephyr valve by Pulmonx. Endobronchial valves are deployed to the bronchi via bronchoscopic guidance, and limit airflow to the portions of the lung distal to the valve while allowing mucus and air movement in the proximal direction. The VENT study, the largest endobronchial valve trial using the Zephyr valve, was published in 2010 [5]. This study demonstrated the efficacy of endobronchial valve treatment, especially in patients with heterogeneous emphysema and complete interlobar fissures as opposed to homogeneous emphysema and incomplete interlobar fissures. Subsequent studies demonstrated the importance of absence of collateral ventilation, measured by the Chartis system, when considering endobronchial valves [6].

The current study by Kemp et al is the first multicenter randomized endobronchial valve trial conducted in Europe. The study was able to demonstrate remarkable improvement in FEV1 (mean 140 mL decrease vs 90 mL increase) and 6-minute walk distance (mean +36.2 meter vs –42.5 meter) after endobronchial valve treatment in severe emphysema patients. The amount of volume reduction was reaching up to 2 liters. Patients in the control group were given the opportunity to receive endobronchial valve after the 6 months study follow-up period and 30 out of 32 patients opted for the endobronchial valve treatment. The authors concluded that the endobronchial valve therapy resulted in clinically meaningful benefits in lung function, dyspnea, exercise tolerance and quality of life with an acceptable safety profile.

It is notable that the authors included only selected patients, limited to those with presence of heterogeneous emphysema, absence of collateral ventilation, low risk of COPD exacerbation or infection, and patients who were likely able to tolerate pneumothorax. Despite this, 13 patients developed pneumothorax and death occurred in 1 patient, leading to a significantly longer average length of hospital stay in the treatment group. Although this rate of complications is not higher than prior endobronchial valve studies, it is important to note when broadly

applying the outcomes of this study to patient care. Lack of long-term follow-up and the nonblinded study design also limit the strength of this study.

Applications for Clinical Practice

Many patients suffer from emphysema. Among them, severe emphysema is the most difficult to manage. It is important to incorporate optimal medical management including bronchodilators, palliative care, oxygen therapy, pulmonary rehabilitation and non-invasive ventilation options. When patients with severe emphysema continue to decline or seek further improvement in their care, and when they meet the specific criteria for lung volume reduction, endobronchial valve therapy should be considered an option and physicians should refer them to appropriate centers. However, the risk of complications, such as pneumothorax, still remains high.

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Brentuximab Vedotin with Chemotherapy Improves Progression-Free Survival in Advanced-Stage Hodgkin's Lymphoma

Connors JM, Jurczak W, Straus DJ, et al. Brentuximab vedotin with chemotherapy for stage III or IV Hodgkin's lymphoma. N Engl J Med 2017 Dec 10.

Study Overview

Objective. To compare the efficacy of brentuximab vedotin, doxorubicin, vinblastine, and dacarbazine (A+AVD) with that of doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) in patients with stage III or IV classic Hodgkin's lymphoma.

Design. The ECHELON-1 trial, an international, open-label, randomized phase 3 trial.

Setting and participants. In this multicenter international trial, a total of 1334 patients underwent randomization from November 2012 through January 2016. Eligible patients were 18 years of age older and had newly diagnosed and histologically proven classic Hodgkin's lymphoma, Ann Arbor stage III or IV. Patients were eligible only if they had not received prior systemic chemotherapy or radiotherapy. All patients were required to have an ECOG performance status of ≤ 2 and adequate hematologic parameters (hemoglobin ≥ 8, ANC ≥ 1500, and platelet count ≥ 75,000). Patients with nodular lymphocyte predominant Hodgkin's lymphoma, pre-existing peripheral sensory neuropathy, or known cerebral or meningeal disease were excluded.

Intervention. Patients were randomized in a 1:1 fashion to receive A+AVD (brentuximab vedotin 1.2 mg/kg, doxorubicin 25 mg/m^2, vinblastine 6 mg/m^2 and dacarbazine 375 mg/m^2) or ABVD (doxorubicin 25 mg/m^2, bleomycin 10 units/m^2, vinblastine 6 mg/m^2 and

dacarbazine 375 mg/m^2) IV on days 1 and 15 of each 28-day cycle for up to 6 cycles. A PET scan was done at the end of the second cycle (PET2) and if this showed increased uptake at any site or uptake at a new site of disease (Deauville score 5) patients could be switched to an alternative frontline therapy at the treating physician's discretion.

Main outcome measures. The primary endpoint of this study was modified progression-free survival (mPFS), defined as time to disease progression, death, or modified progression (noncomplete response after completion of frontline therapy—Deauville score 3, 4, or 5 on PET). Modified progression was incorporated as an endpoint in order to assess the effectiveness of frontline therapy. A secondary endpoint of the study was overall survival (OS).

Results. The baseline characteristics were well balanced between the treatment arms. 58% of the patients were male and 64% had stage IV disease. The median age was 36 years and 9% in each group were over the age of 65. After a median follow-up of 24.9 months, the independently assessed 2-year mPFS was 82.1% and 77.2% in the A+AVD and ABVD groups, respectively (hazard ratio [HR] 0.77; 95% confidence interval [CI] 0.6–0.98). The 2-year mPFS rate according to investigator assessment was 81% and 74.4% in the A+AVD and ABVD groups, respectively. Modified progression (failure to achieve a complete response after completion of frontline therapy resulting in treatment with subsequent therapy) occurred in 9 and 22 patients in the A+AVD and ABVD groups, respectively. A pre-specified subgroup analysis showed that patients from North America, male patients, patients with involvement of more than 1 extranodal site, patients with a high IPSS score (4–7), patients < 60 years old and those with stage IV disease appeared to benefit more from A+AVD. The rate of PET2 negativity was 89% with A+AVD and 86% with ABVD. The 2-year overall survival was 96.6% in the A+AVD group and 94.9% in the ABVD group (HR 0.72; 95% CI 0.44–1.17). Fewer patients in the A+AVD group received subsequent cancer-directed therapy.

Neutropenia was more commonly reported in the A+AVD group (58% vs. 45%). Moreover, febrile neutropenia was reported in 19% and 8% of patients in the A+AVD and ABVD groups, respectively. Discontinuation rates in either arm for febrile neutropenia was ≤ 1%. The rate of infections was 55% in the A+AVD group and 50% in the ABVD group (grade 3 or higher: 18% and 10%, respectively). After review of the rates of febrile neutropenia, the safety monitoring committee recommended that primary prophylaxis with granulocyte colony-stimulating factor (G-CSF) be used for patients who were yet to be enrolled. The rate of febrile neutropenia in the 83 patients in the A+AVD group who received primary prophylaxis was lower than those who did not (11% vs. 18%). Peripheral neuropathy occurred in 67% of patients in the A+AVD group and 42% in the ABVD group (grade 3 or higher: 11% vs 2%, respectively). Neuropathy lead to discontinuation of a study drug in 10% of patients in the A+AVD group. 67% of patients with peripheral neuropathy in the A+AVD group had resolution or improvement by one grade of their neuropathy at the time of last follow up. Pulmonary toxicity was reported in 2% of patients in the A+AVD group and 7% of the ABVD group (grade 3 or higher: < 1% vs. 3%, respectively). During treatment, 9 deaths were reported in the A+AVD group and 13 deaths in the ABVD group. Of the deaths in the ABVD group, 11 were associated with pulmonary toxicity.

Conclusion. A+AVD had superior efficacy to ABVD in the treatment of patients with advanced-stage Hodgkin's lymphoma.

Commentary

Hodgkin's lymphoma (HL) accounts for approximately 10% of all lymphomas in the world annually [1]. While outcomes with frontline therapy for patients with HL have dramatically improved with ABVD, up to 30% of patients have either refractory disease or relapse after initial therapy [2,3]. One particular area of concern in the current treatment of HL with ABVD is the associated pulmonary toxicity of bleomycin. Pulmonary toxicity from bleomycin occurs in approximately 20%–30% of patients and can lead to long-term morbidity [4,5]. In addition, approximately 15% or more of HL patients are elderly and may have co-existing pulmonary disease. In the previously published E2496 trial, the risk of bleomycin lung toxicity in the elderly was 24% [3]. Although the risk of clinically relevant lung toxicity remains low, there is considerable concern about this amongst clinicians. Recent data has challenged the benefit of bleomycin as a component of ABVD. For example, Johnson and colleagues have shown that in patients with a nega-

tive PET scan after 2 cycles of ABVD, the omission of bleomycin (ie, continuation of AVD) resulted in only a 1.6% reduction in 3-year progression-free survival with a decrease in pulmonary toxicity [6].

Recently, there have been notable advances in the treatment of patients with relapsed or refractory HL, including the incorporation of the PD-1 inhibitor nivolumab as well as the immunotoxin conjugated CD30 monoclonal antibody brentuximab vedotin (BV). Given the activity of such agents in relapsed and refractory patients, there has been much enthusiasm about incorporation of such agents into the frontline setting. In the current ECHELON-1 trial, Connors and colleagues present the results of a randomized phase 3 trial comparing ABVD, the current standard of care, to A+AVD, which replaces bleomycin with BV. The trial used a primary endpoint of modified progression-free survival, where a noncomplete response and after primary therapy and subsequent treatment with anticancer therapy was considered disease progression. Notably, this trial did meet its primary endpoint of improved modified PFS, with a 4.9% lower risk of progression, death, or noncomplete response and subsequent need for treatment at 2 years. Overall survival was not significantly different at the time of analysis.

There are some noteworthy findings in addition to this. First, A+AVD was associated with a higher risk of febrile neutropenia and infectious complications; however, following the incorporation of G-CSF prophylaxis this risk was lowered. The pulmonary toxicity was lower in the A+AVD group (2% vs. 7%). A+AVD was associated with an increased risk of peripheral neuropathy, which appeared to improve or resolve following discontinuation of therapy. The neuropathy was mainly low grade with only 11% being grade 3 or higher. Although it remains early and follow-up short, A+AVD did appear to have superior efficacy with a decrease in the risk of pulmonary toxicity in this study. It is worth noting that the risk of neurotoxicity was higher, albeit reversible with drug discontinuation. Given these results, A+AVD warrants consideration as frontline therapy in newly diagnosed patients with advanced stage classic Hodgkin's lymphoma.

Applications for Clinical Practice

The results of this trial suggest that A+AVD with G-CSF support compares favorably to ABVD and may represent an acceptable first-line treatment strategy, particularly for patients at higher risk for pulmonary toxicity, although follow-up remains short at this time.

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