Adjuvant Pembrolizumab Improves Progression-Free Survival in Stage III Melanoma

Eggermont AMM, Blank CU, Mandala M, et al. Adjuvant pembrolizumab versus placebo in resected stage III melanoma. N Engl J Med 2018;378:1789–1801.

Study Overview

Objective. To evaluate pembrolizumab as adjuvant therapy for patients with resected, high-risk stage III melanoma.

Design. International randomized phase 3 trial.

Setting and participants. This multicenter international trial enrolled patients who had histologically confirmed cutaneous melanoma with regional lymph node metastasis (stage IIIA, IIIB or IIIC with no in-transit metastases). Patients had to have undergone a complete regional lymphadenectomy within 13 weeks before the start of treatment. Exclusion criteria were: ECOG performance status score > 1, autoimmune disease, current steroid use, and prior systemic therapy for melanoma. All tumor samples from melanoma-positive lymph nodes were required to be sent to the central lab for evaluation of programmed death ligand 1 (PD-L1) expression; PD-L1 positivity was defined as a tumor proportion score (TPS) ≥ 1%.

Intervention. Patients were randomized in a 1:1 fashion and stratified according to stage and geographic region. Local pharmacies were aware of trial-group assignments. Patients received either an intravenous infusion of pembrolizumab 200 mg or placebo every 3 weeks for a total of 18 doses or until disease recurrence or unacceptable toxicity occurred. If recurrence was detected, patients were able to cross over.

Main outcome measures. The primary outcome was recurrence-free survival (RFS) in the intention-to-treat population and in the subgroup of PD-L1–positive patients. Secondary endpoints included distant metastasis–free survival, overall survival (OS), safety, and quality of life.

Results. A total of 1019 patients were recruited from 123 centers in 23 countries: 514 were assigned to the pembrolizumab group and 505 were assigned to the placebo group. In the pembrolizumab group, 70 patients (13.8%) discontinued treatment because of an adverse event; in 66 patients of these patients the event was deemed drug-related. In the placebo group, 11 (2.2%) patients discontinued treatment due to an adverse event. Discontinuation due to disease recurrence was seen in 109 (21%) patients in the pembrolizumab group and 179 (35.7%) patients in the placebo group. The median duration of follow up was 15 months. In the overall intention-to-treat population, the 12-month RFS rate was 75.4% in the pembrolizumab group versus 61% in the placebo group

($P < 0.001$). At 18 months the RFS rates were 71.4% and 53.2%, respectively. The 18-month incidence of distant metastasis at recurrence was lower in the pembrolizumab group (16.7% vs. 29.7%, hazard ratio [HR] 0.53; 95% confidence interval 0.37 to 0.76). In those who were PD-L1–positive ($n = 853$), the 12-month RFS rate was 77.1% in the pembrolizumab group versus 62.6% in the placebo group. PD-L1 status had no impact on pembrolizumab efficacy. The benefit of pembrolizumab was noted across all subgroups, and no difference was seen in patients with stage IIIA, IIIB or IIIC disease. The benefit of pembrolizumab was similar in those with macroscopic or microscopic nodal metastasis. *BRAF* status did not influence RFS between the pembrolizumab and placebo groups.

Adverse events of grade 3 or higher were seen in 14.7% and 3.4% of the pembrolizumab and placebo groups, respectively. Immune-related adverse events of any grade were noted in 37% of patients in the pembrolizumab group. There was 1 pembrolizumab-related death secondary to myositis. Grades 3 or 4 immune-related events in the pembrolizumab group occurred at a low rate, including colitis (2% and 0.2%), hypophysitis (0.6% and 0%), and type 1 diabetes mellitus (1% and 0%).

Conclusion. Adjuvant pembrolizumab for patients with high-risk stage III melanoma significantly improved RFS compared with placebo and should be considered as an option for adjuvant therapy in this patient population.

Commentary

Prior to the development of immune checkpoint inhibitors, high-dose interferon alfa was the sole option for adjuvant therapy in high-risk melanoma. Although adjuvant interferon alfa is associated with improvements in disease-free survival [1], it is also associated with significant toxicity, including myelosuppression, neurologic adverse effects, and hepatotoxicity. The development of checkpoint inhibition represents an important advancement in the management of patients with melanoma. In the previously reported EORTC 18071 trial, Eggermont and colleagues demonstrated that adjuvant therapy with the CTLA-4 antibody ipilimumab improved both RFS (41% vs. 30%) and OS (65% vs. 54%) at 5 years in patients with stage III melanoma [2]. In 2017, Weber and colleagues demonstrated superior RFS (70% vs. 60%) and a lower rate of grade 3 or 4 adverse events with adjuvant nivolumab compared to ipilimumab in the CheckMate-238 trial [3].

In the current article, Eggermont and colleagues present the results of the EORTC 1325/KEYNOTE-054 study comparing the use of the PD-1 antibody pembrolizumab to placebo in the adjuvant setting for stage III melanoma. This study demonstrated a 43% reduced risk of recurrence or death favoring the pembrolizumab group (HR 0.57; $P < 0.001$). The 12-month RFS was 75.4% in the pembrolizumab arm versus 61% in the placebo arm. Treatment-related adverse events of grade 3 or higher occurred more commonly in the pembrolizumab arm (14.7% vs. 3.4%), with approximately 7% of these patients experiencing a grade 3 or higher immune-related adverse event. The results of this study corroborate prior data on the efficacy of PD-1 inhibitors in melanoma. Also, the investigators assessed RFS based on patient's PD-L1 status (positivity defined as TPS ≥ 1%) as a co-primary endpoint, and found consistent efficacy regardless of PD-L1 expression, with a hazard ratio of 0.47 in the 116 patients who had no PD-L1 expression.

Although the results of this study demonstrate a significant increase in RFS associated with adjuvant pembrolizumab therapy, an OS benefit has not yet been demonstrated. As noted, the only adjuvant checkpoint inhibitor trial to demonstrate an OS advantage thus far is the EORTC 18071 study of ipilimumab. However, the toxicity profile of adjuvant ipilimumab makes it an unattractive option compared to the PD-1 inhibitors. Which of the PD-1 inhibitors should be the treatment of choice for adjuvant therapy remains unclear, although it is worth noting that only nivolumab was compared to the best alternate therapy, ipilimumab [3]. It is also important to note that EORTC 1325/KEYNOTE-054 included patients with stage IIIA disease (N1a disease with at least 1 micrometastasis > 1 mm) or stage IIIB or IIIC without in-transit metastases, while CheckMate-238 did not include stage IIIA patients. Thus, for stage IIIA patients pembrolizumab remains the only PD-1 inhibitor with randomized data demonstrating a benefit.

Applications for Clinical Practice

The results from the EORTC 1325/KEYNOTE-054 study demonstrate a 43% reduction in the risk of progression or

death with the use of adjuvant pembrolizumab in patients with stage III melanoma. As of now, the only checkpoint inhibitor to demonstrate an improvement in OS is ipilimumab, and whether the RFS benefit of both pembrolizumab and nivolumab will translate into an OS benefit is yet to be demonstrated.

—Daniel Isaac, DO, MS

References

1. Kirkwood JM, Strawderman MH, Ernstoff MS, et al. Interferon alfa-2b adjuvant therapy of high-risk cutaneous melanoma: the Eastern Cooperative Oncology Group Trial EST 1684. J Clin Oncol 1996;14:7–17.
2. Eggermont AM, Chiarion-Sileni V, Grob JJ, et al. Prolonged survival in stage III melanoma with ipilimumab adjuvant therapy. N Engl J Med 2016;375:1845–55.
3. Weber J, Mandala M, Del Vecchio M, et al. Adjuvant nivolumab versus ipilimumab in resected stage III or IV melanoma. N Engl J Med 2017;377:1824–35.

Nocturnal Dexmedetomidine for Prevention of Delirium in the ICU

Skrobik Y, Duprey MS, Hill NS, Devlin JW. Low-dose nocturnal dexmedetomidine prevents ICU delirium. A randomized, placebo-controlled trial. Am J Respir Crit Care Med. 2018;197:1147-1156.

Study Overview

Objective. To determine if nocturnal dexmedetomidine prevents delirium and improves sleep in critically ill patients.

Design. Two-center, double-blind, placebo-controlled, randomized, trial.

Setting and participants. This study was conducted in the intensive care units (ICU) at 2 centers in North America between 2013 and 2016. Adults admitted to the ICU and receiving intermittent or continuous sedatives and expected to require at least 48 hours of ICU care were included in the study. Exclusion criteria were presence of delirium, severe dementia, acute neurologic injury, severe bradycardia, hepatic encephalopathy, end-stage liver disease, and expected death within 24 hours.

Intervention. Patients were randomized 1:1 to receive nocturnal dexmedetomidine (0.2–0.7 mcg/kg/hr) or dextrose 5% in water. Patients, clinicians, bedside nurses, and all study personnel were blinded to study drug assignment throughout the study. All sedatives were halved before the study drug was administered each evening. As-needed intravenous midazolam was used while titrating up the study drug. Study drug was administered nightly until either ICU discharge or an adverse event occurred. Decisions regarding use of other analgesic and sedative therapy, including opioids, oral benzodiazepines, acetaminophen, and nonsteroidal anti-inflammatory drugs, were left to the discretion of the clinician. Sleep-promoting agents such as melatonin or trazodone were not allowed.

Main outcome measures. The primary outcome was the proportion of patients who remained free of delirium during their critical illness. Secondary outcomes included ICU days spent without delirium; duration of delirium; sleep quality; proportion of patients who ever developed coma; proportion of nocturnal hours spent at each Richmond Agitation and Sedation Scale (RASS) score; maximal nocturnal pain levels; antipsychotic, corticosteroid, and oral analgesic use; days of mechanical ventilation; ICU and hospital stay duration; and ICU and hospital mortality.

Main results. 100 patients were randomized, with 50 patients in each group. 89% of patients were mechanically ventilated, and the Prediction of Delirium in ICU (PRE-DELIRIC) score [1] was 54 in the dexmedetomidine group and 51 in the placebo group. Continuous propofol and fentanyl infusion at randomization was used in 49% and 80%, respectively. Duration of median ICU stay was 10 days in the

dexmedetomidine group and 9 days in the placebo group. More patients in the dexmedetomidine group (40 of 50 patients [80%]) than in the placebo group (27 of 50 patients [54%]) remained free of delirium (relative risk [RR], 0.44, 95% confidence interval {CI} 0.23 to 0.82; $P = 0.006$). The median (interquartile range [IQR]) duration of the first episode of delirium was similar between the dexmedetomidine (IQR 2.0 [0.6–2.7] days) and placebo (2.2 [0.7–3.2] days) groups ($P = 0.73$). The average Leeds Sleep Evaluation Questionnaire score also was similar (mean difference, 0.02, 95% CI 0.42 to 1.92) between the 2 groups. Incidence of hypotension or bradycardia did not differ significantly between the groups.

Conclusion. Nocturnal administration of low-dose dexmedetomidine in critically ill adults reduces the incidence of delirium during the ICU stay, and patient-reported sleep quality appears unchanged.

Commentary

Delirium is a sudden state of confusion and/or disturbance of consciousness and cognition that is believed to result from acute brain dysfunction, including neurochemical disequilibrium. It often occurs in association with a general medical condition, such as various types of shock, sepsis, surgery, anesthesia, or electrolyte imbalance. Studies have shown that delirium is associated with increased mortality in critically ill patients [2]. Most ICUs use a systematic assessment tool for early detection of delirium, such as the Confusion Assessment Method for the ICU (CAM-ICU), the Intensive Care Delirium Screening Checklist (ICDSC), or the *DSM-IV TR* score system. The CAM-ICU is the most frequently used tool to evaluate for the presence of delirium in critically ill patients; it is scored as positive if the patient manifests both an acute change in mental status and inattention, and has either a RASS greater than 0 or disorganized thinking [3].

The level of evidence regarding delirium prevention is low. Ear plugs, eye masks, educational staff, supportive reorientation, and music have been studied as nonpharmacologic methods for preventing delirium [4]. From a pharmacologic standpoint, the dopamine D2 antagonist haloperidol has been explored as a therapy for both treating and preventing delirium, since the condition is thought to be associated with anticholinergic and excessive dopaminergic mechanisms. A randomized controlled study in 142 patients who received haloperidol 2.5 mg intravenously every 8 hours found that the duration of delirium did not differ between the haloperidol and the placebo groups [5]. The most feared adverse effects of haloperidol, such as akathisia, muscle stiffness, arrhythmia, or QT prolongation, did not occur more frequently in the haloperidol group. Similar results have been reported by Al-Qadheeb et al [6]. Pharmacologic prophylaxis of delirium using atypical antipsychotics such as quetiapine has also been explored, but the level of evidence for this intervention remains very low. Current American College of Critical Care Medicine guidelines recommend nonpharmacologic management and do not firmly recommend any pharmacologic prevention for ICU delirium [7].

Dexmedetomidine is a selective alpha-2 adrenergic receptor agonist that acts at the locus ceruleus, providing sedation and analgesia. Studies assessing the choice of sedation in the ICU found that the use of dexmedetomidine or propofol, compared to benzodiazepines, is associated with a lower rate of delirium occurrence, especially in mechanically ventilated patients [8,9]. Dexmedetomidine offers several potential advantages over other sedative drugs: it has little effect on cognition, has minimal anticholinergic effect, and may restore a natural sleep pattern. While propofol causes hypotension, respiratory depression, and deeper sedation, dexmedetomidine is associated with lighter sedation, a minimal effect on respiratory drive, and a milder hemodynamic effect. In a randomized controlled trial involving post-surgery ICU patients, dexmedetomidine partially restored a normal sleep pattern (eg, increased percentage of stage 2 non-rapid eye movement sleep), prolonged total sleep time, improved sleep efficiency, and increased sleep quality [10]; by improving overall sleep quality, dexmedetomidine potentially may prevent delirium. Another study that randomly assigned 700 ICU patients who underwent noncardiac surgery to dexmedetomidine infusion (0.1 mcg/kg/hr from ICU admission on the day of surgery until the following morning) or placebo reported a significantly reduced incidence of delirium in the dexmedetomidine group [11]. On the other hand, a 2015 Cochrane meta-analysis that included 7 randomized controlled studies did not find a significant risk reduction of delirium with dexmedetomidine [12].

The current study by Skrobik et al was a randomized, placebo-controlled trial that examined the role of nocturnal dexmedetomidine in ICU delirium prevention in 100 ICU patients. Nocturnal administration of low-dose dexmedetomidine led to a statistically significant reduction in delirium incidence compared to placebo (RR of delirium, 0.44, 95% CI 0.23 to 0.82, which is similar to that suggested by previous studies). This study adds additional evidence regarding the use of dexmedetomidine for pharmacologic delirium prevention. It included many mechanically ventilated patients (89% of study population), strengthening the applicability of the result. Mechanical ventilation is a known risk factor for ICU delirium, and therefore this is an important population to study; previous trials largely included patients who were not mechanically ventilated. This study also supports the safety of dexmedetomidine infusion, especially in lower doses in critically ill patients, without significantly increasing the incidence of adverse events (mainly hypotension and bradycardia). The study protocol closely approximated real practice by allowing other analgesics, including opioids, and therefore suggests safety and real world applicability.

There are several confounding issues in this study. The study was blinded, and there was concern that the bedside nurses may have been able to identify the study drug based on the effects on heart rate. In addition, 50% of patients received antipsychotics. While baseline RASS score was significantly different between the 2 groups, patients in the dexmedetomidine group reached a deeper level of sedation during the study. Also, the protocol mandated halving the pre-existing sedative on the night of study drug initiation, which could have led to inadequate sedation in the placebo group. Placebo patients received propofol for a similar duration but at a higher dose compared to dexmedetomidine patients, and midazolam and fentanyl infusion was used in a similar pattern between the groups. The high exclusion rate (71%) limits the ability to generalize the results to all ICU patients.

Applications for Clinical Practice

ICU delirium is an important complication of critical illness and is potentially preventable. Benzodiazepines are associated with an increased risk of delirium, while there has been increasing interest in dexmedetomidine, a selective alpha-2 adrenergic receptor agonist, because of its potential for delirium prevention. Evidence to date does not strongly support routine use of pharmacologic prevention of delirium; however, dexmedetomidine may be an option for sedation, as opposed to benzodiazepines or propofol, in selected patients and may potentially prevent delirium.

—Minkyung Kwon, MD, Neal Patel, MD, and Vichaya Arunthari, MD,
Pulmonary and Critical Care Medicine,
Mayo Clinic Florida, Jacksonville, FL

References

1. van den Boogaard M, Pickkers P, Slooter AJ, et al. Development and validation of PRE-DELIRIC (PREdiction of DELIRium in ICu patients) delirium prediction model for intensive care patients: observational multicentre study. BMJ 2012;344:e420.
2. Slooter AJ, Van De Leur RR, Zaal IJ. Delirium in critically ill patients. Handb Clin Neurol 2017;141:449–66.
3. Ely EW, Inouye SK, Bernard GR, et al. Delirium in mechanically ventilated patients: validity and reliability of the confusion assessment method for the intensive care unit (CAM-ICU). JAMA 2001;286:2703–10.
4. Abraha I, Trotta F, Rimland JM, et al. Efficacy of non-pharmacological interventions to prevent and treat delirium in older patients: a systematic overview. The SENATOR project ONTOP Series. PLoS One 2015;10:e0123090.
5. Page VJ, Ely EW, Gates S, et al. Effect of intravenous haloperidol on the duration of delirium and coma in critically ill patients (Hope-ICU): a randomised, double-blind, placebo-controlled trial. Lancet Respir Med 2013;1:515–23.
6. Al-Qadheeb NS, Skrobik Y, Schumaker G, et al. Preventing ICU subsyndromal delirium conversion to delirium with low-dose IV haloperidol: a double-blind, placebo-controlled pilot study. Crit Care Med 2016;44:583–91.
7. Barr J, Fraser GL, Puntillo K, et al; American College of Critical Care Medicine. Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit. Crit Care Med 2013;41:263–306.
8. Riker RR, Shehabi Y, Bokesch PM, et al. Dexmedetomidine vs midazolam for sedation of critically ill patients: a randomized trial. JAMA 2009;301:489–99.
9. Pandharipande PP, Pun BT, Herr DL, et al. Effect of sedation with dexmedetomidine vs lorazepam on acute brain dysfunction in mechanically ventilated patients: the MENDS randomized controlled trial. JAMA 2007;298:2644–53.
10. Wu XH, Cui F, Zhang C, et al. Low-dose dexmedetomidine improves sleep quality pattern in elderly patients after noncardiac surgery in the intensive care unit: a pilot randomized controlled trial. Anesthesiology 2016;125:979–91.
11. Su X, Meng Z-T, Wu X-H, et al. Dexmedetomidine for prevention of delirium in elderly patients after non-cardiac surgery: a randomised, double-blind, placebo-controlled trial. Lancet 2016;388:1893–1902.
12. Chen K, Lu Z, Xin YC, et al. Alpha-2 agonists for long-term sedation during mechanical ventilation in critically ill patients. Cochrane Database Syst Rev 2015;1:CD010269.