Does Oral Chemotherapy Venetoclax Combined with Rituximab Improve Survival in Patients with Relapsed or Refractory Chronic Lymphocytic Leukemia?

Seymour JF, Kipps TJ, Eichhorst B, et al. Venetoclax-rituximab in relapsed or refractory chronic lymphocytic leukemia. N Engl J Med 2018;378:1107–20.

Study Overview

Objective. To assess whether a combination of venetoclax with rituximab, compared to standard chemoimmunotherapy (bendamustine with rituximab), improves outcomes in patients with relapsed or refractory chronic lymphocytic leukemia.

Design. International, randomized, open-label, phase 3 clinical trial (MURANO).

Setting and participants. Patients were eligilble for the study if they were 18 years of age or older with a diagnosis of relapsed or refractory chronic lymphocytic leukemia that required therapy, and had received 1 to 3 previous treatments (including at least 1 chemotherapy-containing regimen), had an Eastern Cooperative Oncology Group performance status score of 0 or 1, and had adequate bone marrow, renal, and hepatic function. Patients were randomly assigned either to receive venetoclax plus rituximab or bendamustine plus rituximab. Randomization was stratified by geographic region, responsiveness to previous therapy, as well as the presence or absence of chromosome 17p deletion.

Main outcome measures. Primary outcome was investigator-assessed progression-free survival, which was defined as the time from randomization to the first occurrence of disease progression or relapse or death from any cause, whichever occurs first. Secondary efficacy endpoints included independent review committee-assessed progression-free survival (stratified by chromosome 17p deletion), independent review committee-assessed overall response rate and complete response rate, overall survival, rates of clearance of minimal residual disease, the duration of response, event-free survival, and the time to the next treatment for chronic lymphocytic leukemia.

Main results. From 31 March 2014 to 23 September 2015, a total of 389 patients were enrolled at 109 sites in 20 countries and were randomly assigned to receive venetoclax plus rituximab (n = 194), or bendamustine plus rituximab (n = 195). Median age was 65 years (range, 22–85) and a majority of the patients (73.8%) were men. Overall, the demographic and disease characteristics of the 2 groups were similar at baseline.

The median follow-up period was 23.8 months (range, 0–37.4). The median investigator-assessed pro-

gression-free survival was significantly longer in the venetoclax-rituximab group (median progression-free survival not reached, 32 events of progression or death in 194 patients) and was 17 months in the bendamustine-rituximab group (114 events in 195 patients). The 2-year rate of investigator-assessed progression-free survival was 84.9% (95% confidence interval [CI] 79.1–90.5) in the venetoclax-rituximab group and 36.3% (95% CI 28.5–44.0) in the bendamustine-rituximab group (hazard ratio for progression or death, 0.17; 95% CI 0.11 to 0.25; $P < 0.001$). Benefit was consistent in favor of the venetoclax-rituximab group in all prespecified subgroup analyses, with or without chromosome 17p deletion.

The rate of overall survival was higher in the venetoclax-rituximab group than in the bendamustine-rituximab group, with 24-month rates of 91.9% and 86.6%, respectively (hazard ratio 0.58, 95% CI 0.25–0.90). Assessments of minimal residual disease were available for 366 of the 389 patients (94.1%). On the basis of peripheral-blood samples, the venetoclax-rituximab group had a higher minimal residual disease compared to the bendamustine-rituximab group (121 of 194 patients [62.4%] vs. 26 of 195 patients [13.3%]). In bone marrow aspirate, higher rates of clearance of minimal residual disease was seen in the venetoclax-rituximab group (53 of 194 patients [27.3%]) as compared to the bendamustine-rituximab group (3 of 195 patients [1.5%]).

In terms of safety, the most common adverse event reported was neutropenia (60.8% of the patients in the venetoclax-rituximab group vs. 44.1% of the patients in the bendamustine-rituximab group). This contributed to the overall higher grade 3 or 4 adverse event rate in the venetoclax-rituximab group (159 of the 194 patients, or 82.0%) as compared to the bendamustine-rituximab group (132 of 188 patients, or 70.2%). The incidence of serious adverse events, as well as adverse events that resulted in death were similar in the 2 groups.

Conclusion. For patients with relapsed or refractory chronic lymphocytic leukemia, venetoclax plus rituximab resulted in significantly higher rates of progression-free survival than standard therapy with bendamustine plus rituximab.

Commentary

Despite advances in treatment, chronic lymphocytic leukemia remains incurable with conventional chemoimmunotherapy regimens, and almost all patient relapse after initial therapy. Following relapse of the disease, the goal is to provide durable progression-free survival, which may extend overall survival [1]. In a subset of chronic lymphocytic leukemia patients with deletion or mutation of TP53 loci on chromosome 17p13, their disease responds especially poorly to conventional treatment and they have a median survival of less than 3 years from the time of initiating first treatment.

Apoptosis defines a process of programmed cell death with an extrinsic and intrinsic cellular apoptotic pathway. B-cell lymphoma/leukemia 2 (BCL-2) protein is a key regulator of the intrinsic apoptotic pathway and almost all chronic lymphocytic leukemia cells elude apoptosis through overexpression of BCL-2. Venetoclax is an orally administered, highly selective, potent BCL-2 inhibitor approved by the FDA in 2016 for the treatment of chronic lymphocytic leukemia patients with 17p deletion who have received at least 1 prior therapy [3]. There has been great interest in combining venetoclax with other active agents in chronic lymphocytic leukemia such as chemotherapy, monoclonal antibodies, and B-cell receptor inhibitors. The combination of venetoclax with the CD20 antibody rituximab was found to be able to overcome micro-environment-induced resistance to venetoclax [4].

In this analysis of the phase 3 MURANO trial of venetoclax plus rituximab in relapsed or refractory chronic lymphocytic leukemia by Seymour et al, the authors demonstrated a significantly higher rate of progression-free survival with venetoclax plus rituximab than with standard chemoimmunotherapy bendamustine plus rituximab. In addition, secondary efficacy measures, including the complete response rate, the overall response rate, and overall survival were also higher in the venetoclax plus rituximab than with bendamustine plus rituximab.

There are several limitations of this study. First, this study was terminated early at the time of the data review on 6 September 2017. The independent data monitoring committee recommended that the primary analysis be conducted at that time because the prespecified statistical boundaries for early stopping were crossed for progression-free survival on the basis of stratified log-rank

tests. In a letter to the editor, Alexander et al questioned the validity of results when design stages are violated. In immunotherapy trials, progression-free survival curves often separated at later time, rather than as a constant process; this violates the key assumption of proportionality of hazard functions. When the study was terminated early, post hoc confirmatory analyses and evaluations of robustness of the statistical plan could be used; however, prespecified analyses are critical to reproducibility in trials that are meant to be practice-changing [5]. Second, complete response rates were lower when responses was assessed by the independent review committee than when assessed by the investigator. While this represented a certain degree of author bias, the overall results were similar and the effect of venetoclax plus rituximab remain significantly better than bendamustine plus rituximab.

Applications for Clinical Practice

The current study demonstrated that venetoclax is safe and effective when combining with rituximab in the treating of chronic lymphocytic leukemia patients with or without 17p deletion who have received at least one prior therapy. The most common serious adverse event was neutropenia, correlated with tumor lysis syndrome. Careful monitoring, slow dose ramp-up, and adequate prophylaxis can mitigate some of the adverse effects.

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Non-Culprit Lesion PCI Strategies in Patients with Acute Myocardial Infarction and Cardiogenic Shock Revisited

Lee JM, Rhee TM, Hahn JY; KAMIR Investigators. Multivessel percutaneous coronary intervention in patients with ST-segment elevation myocardial infarction with cardiogenic shock. J Am Coll Cardiol 2018;71:844–56.

Study Overview

Objective. To determine the prognostic impact of multivessel percutaneous coronary intervention (PCI) in patients with ST-segment elevation myocardial infarction (STEMI) multivessel disease presenting with cardiogenic shock.

Design. Retrospective study using the nationwide, multicenter, prospective KAMIR-NIH (Korea Acute Myocardial Infarction-National Institutes of Health) registry.

Setting and participants. Among the 13,104 patients enrolled in the KAMIR-NIH registry, 659 patients with STEMI with multivessel disease presenting with cardiogenic shock who underwent primary PCI were selected.

Main outcome measures. The primary outcome was all-cause death at 1 year. Secondary outcomes included patient-oriented composite outcome (composite of all-cause death, any myocardial infarction, and any repeat revascularization) and its individual components.

Main results. A total of 260 patients were treated with multivessel PCI and 399 patients were treated with infarct-related artery (IRA) PCI only. The risk of all-cause death was significantly lower in the multivessel PCI group (21.3% vs 31.7%; hazard ratio [HR] 0.59, 95% CI 0.43–0.82, *P* = 0.001). Non-IRA repeat revascularization was significantly lower in the multivessel group (6.7% vs 8.2%; HR 0.39, 95% CI 0.17–0.90, *P* = 0.028). In multivariate model, multivessel PCI was independently associated with reduced risk of 1-year all-cause death and patient-oriented composite outcome.

Conclusion. Among patients with STEMI and multivessel disease with cardiogenic shock, multivessel PCI was associated with significantly lower risk of all-cause death and non-IRA repeat revascularization.

Commentary

Historically, non-culprit vessel revascularization in the setting of acute myocardial infarction (AMI) was not routinely performed. However, recent trials have shown the benefit of non-culprit vessel revascularization in patients with hemodynamically stable AMI [1–3]. The result of these trials have led to upgrade in U.S. guideline recommendations for non-infarct-related artery PCI in hemodynamically stable patients presenting with AMI to Class IIb from Class III [4]. Whether these findings can be extended to hemodynamically unstable (cardiogenic shock) patients is controversial. Recently, results of a well-designed randomized control trial (CULPRIT-SHOCK) suggested worse outcome with immediate multivessel PCI in this population [5]. The composite endpoint of death and renal replacement therapy at 30 days was higher in the multivessel PCI at the time of primary PCI group compared to initial culprit lesion only group (55.9% vs 45.9%, *P* = 0.01). The composite endpoint was mainly driven by death (51.6% vs 43.3%, *P* = 0.03), and the rate of renal replacement therapy was numerically higher in the mutivessel PCI group (16.4% vs 11.6%, *P* = 0.07).

Lee et al investigated a similar clinical question using the nationwide, multicenter, prospective KAMIR-NIH registry data [6]. In this study, the primary endpoint of all cause death occurred in 53 of the 260 patients (21.3%) in the multivessel PCI group and 126 of the 399 patients (31.7%) in the IRA-only PCI group (relative risk [RR] 0.59, 95% CI 0.43–0.82, *P* = 0.001). Similarly, the multivessel PCI group had lower non-IRA repeat revascularization (RR 0.39, 95% CI 0.17-0.90, *P* = 0.028) and lower patient-oriented composite outcome (all-cause death, any myocardial infarction, or any repeat revascularization) (RR 0.58, 95% CI 0.44–0.77, *P* < 0.001). These results remained similar after multivariate adjustment, propensity matching, and inverse probability weighted analysis.

The discrepancy of the results of the KAMIR study compared to CULPRIT-SHOCK is likely related to the difference in the design of the two studies. First, CUPRIT-SHOCK compared multivessel revascularization during index primary PCI to culprit-only revascularization strategy with staged revascularization if necessary. There were 9.4% randomized to multivessel PCI who crossed over to IRA-only PCI and 17.4% randomized to IRA-only PCI who crossed over to multivessel PCI during the index hospitalization. In contrast, the KAMIR registry compared patients who underwent IRA-only PCI to multivessel PCI, which included those who had immediate revascularization during the primary PCI and those who had staged revascularization during the index hospitalization. Therefore, multivessel PCI is defined very differently in both studies and cannot be considered equivalent.

Second, CULPRIT-SHOCK was a prospective randomized control study and KAMIR was an observational study analyzing data from a prospectively collected large database. Although multiple statistical adjustments were performed, this observational nature of the study is subject to selection bias and other unmeasured biases such as frailty assessment.

Third, the timing of the revascularization was different between two studies. In CULPRIT-SHOCK, immediate revascularization of non-IRA was achieved in 90.6% of patients in the multivessel PCI group. On the other hand, only 60.4% of patients of multivessel PCI group in KAMIR study underwent immediate revascularization of the non-IRA and 39.6 % of patients underwent staged procedure. This leads to significant survival bias, since these 39.6% of patients survived the initial event to be able to undergo the staged procedure. Patients who had planned staged intervention but could not survive were included in the IRA-only PCI group.

Fourth, there may be difference in the severity of the patient population included in the analysis. In the CUL-

PRIT-SHOCK trial, a significant non-IRA was defined as > 70% stenosis, and all chronic total occlusions (CTO) were attempted in the multivessel PCI group according to trial protocol. In CULPRIT-SHOCK, 23% of patient had one or more CTO lesions. In the KAMIR registry, a significant non-IRA was defined as > 50% stenosis of the non-culprit vessel and CTO vessels were not accounted for. Although CTO intervention improves angina and ejection fraction [7,8], whether CTO intervention has mortality benefit needs further investigation. In a recent EXPLORE trial, the feasibility and safety of intervention of chronic total occlusion in non-infarct-related artery in STEMI population was established [8]. However, only hemodynamically stable patients were included in the study and all CTO interventions were performed in staged fashion (5 ± 2 days after index procedure) [8]. There is a possibility of attempting CTO PCI in this acute setting caused more harm than benefit.

Finally, in order to be enrolled in the CULPRIT-SHOCK trial, patients needed to meet stringent criteria for cardiogenic shock. In KAMIR study, this data was retrospectively determined and individual components used to define cardiogenic shock were not available. This difference may have led to inclusion of more stable patients as evidenced by lower mortality rate in KAMIR study compared to CULPRIT-SHOCK (51.6% mortality for multivessel PCI in CULPRIT-SHOCK and 21.3% mortality for multivessel PCI patients in KAMIR study). CULPRIT-SHOCK trial had a high rate of mechanical ventilation (~80%), requirement of catecholamine support (~90%), and long ICU stays (median 5 days). This information is not reported in the KAMIR study.

Considering above differences in the study design, the evidence level for CULPRIT-SHOCK appears to be stronger compared to the KAMIR study, which should be considered as hypothesis-generating as all other observational studies. However, the KAMIR study is still an important study suggesting possible benefit of multivessel PCI in patients presenting with ST elevation myocardial infarction and cardiogenic shock. This leads us to an answered question whether staged multivessel intervention or less aggressive multivessel intervention (not attempting CTO) is a better option in this population.

Applications for Clinical Practice

In patients presenting with cardiogenic shock and acute myocardial infarction, culprit lesion-only intervention and staged intervention if necessary, seems to be a better strategy. However, there may be benefit in multivessel intervention in this population, depending on the timing and revascularization strategy. Further studies are needed.

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Balanced Crystalloids in the Critically Ill

Semler MW, Self WH, Wanderer JP, et al; SMART Investigators and the Pragmatic Critical Care Research Group. Balanced crystalloids versus saline in critically ill adults. N Engl J Med 2018;378:829–39.

Study Overview

Objective. To evaluate balanced crystalloids in comparison with normal saline in the intensive care unit (ICU) population.

Design. Pragmatic, un-blinded, cluster-randomized, multiple-crossover clinical trial (the SMART study).

Setting and participants. The study evaluated critically ill adults > 18 years of age, admitted and readmitted into 5 ICUs, both medical and surgical, from June 2015 to April 2017. 15,802 patients were enrolled, powered to detect a 1.9% percentage point difference in primary outcome. ICUs were randomized to use either balanced crystalloids (lactated Ringer's [LR] or Plasma-Lyte A, depending on the provider's preference) or normal saline during alternate calendar months. Relative contraindications to use of balanced crystalloids included traumatic brain injury and hyperkalemia. The admitting emergency rooms and operating rooms coordinated intravenous fluid (IVF) choice with their respective ICUs. An intention-to-treat analysis was conducted. In addition to primary and secondary outcome analyses, subgroup analyses based on factors including total IVF volume to day 30, vasopressor use, predicted in-hospital mortality, sepsis or traumatic brain injury diagnoses, ICU type, source of admission, and kidney function at baseline were also done. Furthermore, sensitivity analyses taking into account the total volume of crystalloid, crossover and excluding readmissions were performed.

Main outcome measures. The primary outcome was the proportion of patients that met at least 1 of the 3 criteria for a Major Adverse Kidney Event at day 30 (MAKE30) or discharge, whichever occurred earlier. MAKE30 is a composite measure consisting of death, persistent renal dysfunction (creatinine ≥ 200% baseline), or new renal replacement therapy (RRT). Patients previously on RRT were included for mortality analysis alone. In addition, secondary clinical outcomes including in-hospital mortality (prior to ICU discharge, at day 30 and day 60), ventilator-free days, vasopressor-free days, ICU-free days, days alive and RRT-free days in the first 28 days were assessed. Secondary renal outcomes such as persistent renal dysfunction, acute kidney injury (AKI) ≥ stage 2 (per Kidney Disease: Improving Global Outcomes Criteria {KDIGO}) criteria, new RRT, highest creatinine during hospitalization, creatinine at discharge and highest change in creatinine during hospitalization were also evaluated.

Results. 7942 patients were randomized to the balanced crystalloid group and 7860 to the saline group. Median age for both groups was 58 years and 57.6% patients were male. In terms of patient acuity, approximately 34% patients were on mechanical ventilation, 26% were on vasopressors, and around 14% carried a diagnosis of sepsis. At time of presentation, 17% had chronic kidney disease (CKD) ≥ stage 3 and approximately 5% were on RRT. Around 8% came in with AKI ≥ stage 2. Baseline creatinine in the both groups was 0.89 (interquartile range [IQR] 0.74–1.1). Median volumes of balanced crystalloid and saline administered was 1L (IQR 0–3.2L) and 1.02L (IQR 0–3.5L) respectively. Less than 5% in both groups received unassigned fluids. Predicted risk of in-hospital death for both groups was approximately 9%.

Significantly higher number of patients had plasma chloride ≥ 110 mmol/L and bicarbonate ≤ 20 mmol/L in the saline group ($P < 0.001$). In terms of primary outcome, MAKE30 rates in the balanced crystalloid vs saline groups were 14.3 vs 15.4 (marginal odds ratio {OR} 0.91, 95% confidence interval {CI} 0.84–0.99, $P = 0.04$) with similar results in the pre-specified sensitivity analyses. This difference was more prominent with larg-

er volumes of infused fluids. All 3 components of composite primary outcome were improved in the crystalloid group, although none of the 3 individually achieved statistical significance.

Overall, mortality before discharge and within 30 days of admission in the balanced crystalloid group was 10.3% compared to 11.1% in the saline group (OR 0.9, CI 0.8–1.01, $P = 0.06$). In-hospital death before ICU discharge and at 60 days also mirrored this trend, although they did not achieve statistical significance either. Of note, in septic patients, 30-day mortality rates were 25.2 vs 29.4 in the balanced crystalloid and saline groups respectively (OR 0.8, 95% CI 0.67–0.97, $P = 0.02$).

With regard to renal outcomes in the balanced crystalloid vs normal saline groups, results were as follows: new RRT {2.5 vs 2.9%, $P = 0.08$}, new AKI development 10.7% vs 11.5% (OR 0.9, $P = 0.09$). In patients with a history of previous RRT or presenting with an AKI, crystalloids appeared to provide better MAKE30 outcomes, although not achieving statistical significance.

Conclusion. In the critically ill population, balanced crystalloids provide a beneficial effect over normal saline on the composite outcome of persistent renal dysfunction, new RRT and mortality at day 30.

Commentary

Unbalanced crystalloids, especially normal saline, are the most commonly used IVF for resuscitation in the critically ill. Given the data suggesting risk of kidney injury, acidosis, and effect on mortality with the use of normal saline, this study aimed to evaluate balanced crystalloids in comparison with normal saline in the ICU population.

Interest in the consequences of hyperchloremia and metabolic acidosis from supra-physiologic chloride concentrations in normal saline first stemmed from data in preclinical models, which demonstrated that chloride-induced renal inflammation adversely impacted renal function and mortality [1,2]. While in theory "balanced" solutions carry dual benefits of both an electrolyte composition that closely mirrors plasma and the presence of buffers which improve acid-base milieu, the exact repercussions on patient-centered outcomes with use of one over the other remain unknown.

An exploratory randomized control trial (RCT) evaluating biochemistry up to day 4 in normal saline vs Plasma-Lyte groups in 70 critically ill adults showed significantly higher hyperchloremia with normal saline but no difference in AKI rates between the two groups [3]. A pilot study evaluating "chloride-restrictive vs chloride liberal" strategies in 760 ICU patients involved use of Hartmann's solution and Plasma-Lyte in place of saline for a 6-month period except in case of specific contraindications such as traumatic brain injury. Results indicated that incidence of AKI and use of RRT significantly reduced by limiting chloride. No changes in mortality, ICU length of stay or RRT on discharge were noted [4]. A large retrospective study in over 53,000 ICU patients admitted with sepsis and on vasopressors across 360 US hospitals showed that balanced fluids were associated with lower in-hospital mortality especially when higher volume of IVFs were infused. While no differences were seen in terms of AKI rates, lower risk of CKD was noted in balanced fluid groups [5].

In post-surgical populations, an observational study analyzing saline vs balanced fluids over 30,000 patients showed significantly lower mortality, renal failure, acidosis investigation/intervention rates with balanced fluids [6]. Additionally, a meta-analysis assessing outcomes in peri-operative and ICU patients based on whether they received high or low chloride containing fluids was performed on over 6000 patients across 21 studies. No association with mortality was found. However, statistically significant correlations were noted between high chloride fluids and hyperchloremia, metabolic acidosis, AKI, mechanical ventilation times and blood transfusion volumes [7].

In 2015, a large RCT involving ICUs in New Zealand evaluated balanced crystalloids vs normal saline and rates of AKI in a double-blind, cluster-randomized, double-crossover trial (the SPLIT study). 2278 patients from medical and surgical ICUs were enrolled. Patients already receiving RRT were excluded. No significant difference in incidence of AKI (defined as a two-fold rise or a 0.5mg/dL increase in creatinine), new RRT or mortality was detected between the two groups [8].

Given the ambiguity and lack of consensus on outcomes, the current SMART study addresses an import-

ant gap in knowledge. Its large sample size makes it well powered, geared to detect small signals in outcomes. Inclusion of medical, surgical, and neurologic ICUs helps diversify applicability. Being a pragmatic, intention-to-treat RCT, the study design mirrors real-world clinical practice.

In terms of patient acuity, less than a third of the patients were intubated or on vasopressors. Predicted mortality rates were 9%. In addition, median volume infused was around 1 L. Given the investigators' conclusions that the MAKE30 outcome signals were more pronounced with larger volumes of infusions, this brings into question whether more dramatic signals could have been appreciated in each of the 3 components of the primary outcome had the study population been a higher acuity group requiring larger infusion volumes.

While the composite MAKE30 outcome reflects a sense of an overarching benefit with balanced crystalloids, there was no statistically significant improvement noted in each primary component. This questions the rationale for combining the components of the MAKE30 outcome as well as how generalizable the results are. Overall, as is the case with many studies that evaluate a composite outcome, this raises concern about overestimation of the intervention's true impact.

The study was un-blinded, raising concern for bias, and it was a single-center trial, which raises questions regarding generalizability. Un-blinding may have played a role in influencing decisions to initiate RRT earlier in the saline group. The extent to which this impacted RRT rates (one of the MAKE30 outcomes), remains unclear. Furthermore, approximately 5% of the participants received unassigned fluids, and while this is in line with the pragmatic/intention-to-treat design, the clinical repercussions remain unclear. Hyperkalemia is an exclusion criterion for balanced fluids and it is unclear whether a proportion of patients presenting with AKI-associated hyperkalemia were restricted from receiving balanced fluids. In addition, very few patients received Plasma-Lyte, confining the study's conclusions to lactated Ringer's alone.

Despite these pitfalls, the study addresses an extremely relevant clinical question. It urges clinicians to tailor fluid choices on a case-by-case basis and pay attention to the long-term implications of daily biochemical changes on renal outcomes, particularly in large volume resuscitation scenarios. There is a negligible cost difference between lactated Ringer's and saline, making use of a balanced fluid economically feasible. The number needed to treat for MAKE30 based on this study is 94 patients, and changes in clinical practice extrapolated to ICUs nationwide could have an impact on renal outcomes from an epidemiologic point of view without risking financial burden at an institution level.

Applications for Clinical Practice

Overall, this trial clarifies an important gap in knowledge regarding fluid choice in the care of critically ill adults. The composite outcome of death, persistent renal dysfunction, and new RRT was significantly lower when a balanced fluid was used in comparison with saline. The ease of implementation, low financial impact, and epidemiologically significant renal outcomes supports a consideration for change in practice. However, clinicians should evaluate implementation on a case-by-case basis. More studies evaluating MAKE30 outcomes individually in specific diagnoses and clinical contexts are necessary. Moreover, data on long-term MAKE outcomes would help characterize long-term public health implications of 30-day effects.

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Nivolumab plus Ipilumumab in NSCLC: A New Use for Tumor Mutational Burden?

Hellmann MD, Ciuleanu TE, Pluzanski A, et al. Nivolumab plus ipilimumab in lung cancer with a high tumor mutational burden. N Engl J Med 2018 Apr 16.

Study Overview

Objective. To examine the effect of nivolumab plus ipilimumab vs nivolumab monotherapy vs standard of care chemotherapy in front line metastatic non-small cell lung cancer (NSCLC).

Design. Multipart phase 3 randomized controlled trial (CheckMate 227 trial).

Setting and participants. Study patients were enrolled at multiple centers around the world. Patients were eligible for enrollment if they had biopsy-proven metastatic NSCLC and had not received prior systemic anti-cancer therapy. Exclusion criteria were patients with known ALK translocations or EGFR mutations, known autoimmune disease, current comorbidity requiring treatment with steroids or other immunosuppression at the time of randomization, or untreated central nervous system (CNS) metastasis. Patients with CNS metastasis could be enrolled if they were adequately treated and had returned to their neurologic baseline.

Intervention. At the time of randomization, patients were split into two treatment groups based on their PD-L1 percentage. Patients with PD-L1 of greater than or equal to 1% were randomly assigned in a 1:1:1 ratio to nivolumab 3 mg/kg every 2 weeks plus ipilimumab 1mg/kg every 6 weeks, nivolumab 240 mg every 2 weeks, or standard chemotherapy based on tumor type (platinum/pemetrexed for non-squamous histology and platinum/gemcitabine for squamous). Patients with PD-L1 less than 1% were randomly assigned in a 1:1:1 ratio to nivolumab 3 mg/kg every 2 weeks plus ipilimumab 1 mg/kg every 6 weeks, nivolumab 360mg every 3 weeks, or standard chemotherapy based on tumor type. Patient's with non-squamous histology that had stable disease or a response to chemotherapy could receive maintenance pemetrexed +/- nivolumab. Patients were followed with imaging every 6 weeks for the first year, then every 12 weeks afterwards. All treatments were continued until disease progression, unacceptable toxicity, or completion of protocol (2 years for immunotherapy).

Main outcome measures. There were 2 co-primary outcomes: Progression-free survival (PFS) of nivolumab/ipilimumab vs chemotherapy in patients selected via tumor mutational burden (TMB), and overall survival in patients selected on PD-L1 status. TMB was defined as 10 or greater mutations per megabase. In this publication, only the first primary end point is reported.

Results. Between August 2015 and November 2016, 2877 patients were enrolled and 1739 were randomized on a 1:1:1 to nivolumab plus ipilimumab, nivolumab monotherapy, or standard of care chemotherapy. Of those, 1004 (57.7%) had adequate data for TMB to be evaluated. Of those, 299 patients met the TMB cutoff for the first primary end point—139 in the nivolumab plus ipilimumab arm and 160 in the chemotherapy arm. The 1-year PFS in patients with a high TMB was 42.6% in the immunotherapy arm vs 13.2% with chemotherapy and the median PFS was 7.2 months vs 5.5 months (hazard ratio [HR] 0.58;

97.5% CI 0.41–0.81; $P < 0.001$). In low TMB patients, the PFS was greater for chemotherapy vs immunotherapy (3.2 vs 5.5 months). The HR for patients with high TMB was significant for all PD-L1 values and for non-squamous histology. For squamous histology, there was a benefit of 12 month PFS of 36% vs 7%, however it was not statistically significant (HR 0.63; 95% CI, 0.39–1.04). In the supplemental index, nivolumab vs chemotherapy with a TMB greater than 13 was shown to have no benefit (HR 0.95; 95% CI 0.64–1.40; $P = 0.7776$).

With regard to adverse events, 31.2% of the nivolumab plus ipilimumab group experienced a grade 3 or greater event vs 36.1% of the chemotherapy group and 18.9% of the nivolumab monotherapy group. Events higher in the combination immunotherapy group were rash (1.6% vs 0%), diarrhea (1.6% vs 0.7%), and hypothyroidism (0.3% vs 0%). Events higher in the chemotherapy arm were anemia (11.2% vs 1.6%), neutropenia/decreased neutrophil count (15.8% vs 0%), nausea (2.1% vs 0.5%), and vomiting (2.3% vs 0.3%).

Conclusion. Among patients with newly diagnosed metastatic NSCLC with tumor mutational burden of 10 or greater mutations per megabase, the combination of nivolumab and ipilimumab resulted in higher progression-free survival than standard chemotherapy.

Commentary

Non-small cell lung cancer is undergoing a renaissance in improved survival as a result of new targeted therapies [1]. Medications to target the epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK) translocations have shown clinical benefit over standard chemotherapy as initial treatment. In addition, in patients with programed death ligand 1 (PD-L1) expression of greater than 50%, pembrolizumab has showed to be superior to standard chemotherapy in the front-line setting. It is currently standard to test all non-squamous lung cancer specimens for EGFR, ALK, and PD-L1, and some argue to test squamous as well. However, through all these treatments, the prognosis of metastatic NSCLC remains poor, as only 4.7% of patients live to 5 years [2].

This study asks if we can add tumor mutational burden (TMB) as actionable information, and should we perform this test on all NSCLC specimens. The theory is that tumors with high TMB will express more foreign antigens, and thus be more responsive to immune checkpoint inhibition. Reviewing the literature, there has been varying correlation between TMB and response to immunotherapy [3]. Despite its potential use as a biomarker, no prior study has shown that using any treatment in a high TMB population conveys any benefit and thus it is not considered standard of care to test for TMB.

This article's conclusion has several major implications. First, does dual immunotherapy have a role in NSCLC? The data in the trial shows that in high TMB patients there is a clear PFS benefit to nivolumab plus ipilimumab over chemotherapy. In addition, about 40% of patients had a durable response at 2 years follow-up. Strengths of this study are the large size, although smaller when selected for only high TMB patients. Another strength is the long follow-up with a minimum of 11.2 months, with a significant number followed for about 2 years. A weakness of this trial is that patients were randomized before their TMB status was known. In addition, only 57.7% of the randomized patients were able to be analyzed for TMB. The third arm of this study (nivolumab monotherapy), while providing the information that it is less effective in this population, does cloud the information. Finally, while a benefit in PFS was found in the TMB cohort, this does not always correlate with an OS benefit in mature data.

Second, if it does have a role, should TMB be a standard test on all NSCLC specimens? While it was borderline, there was no benefit to squamous histology. In the supplemental index it was reported that nivolumab monotherapy did not show a benefit, thus the need to offer ipilimumab depends on TMB status. Pembrolizumab is already approved in patients with PD-L1 expression greater than 50% [2]. However, in patients with PD-L1 less than 50% and no ALK or EGFR mutation, chemotherapy would be frontline treatment; with TMB testing these patients could be spared this toxic treatment. In addition, a parallel published study shows benefit to adding pembrolizumab to standard chemotherapy [4].

Another consideration is the requirements of tissue for testing TMB. This study used the Foundation One assay. This test required optimally 25 square millimeters of tissue and preferred the whole block of tissue or 10 unstained slides [5]. For patients who are diagnosed with

full surgical resection this is not an issue and should not be a barrier for this therapy. However, metastatic disease patients are often diagnosed on core biopsy of a metastatic site, thus getting an accurate TMB profile (in addition to testing other actionable mutations) could be a challenge. Identifying patients who would be a candidate for this therapy prior to biopsy will be important given the tissue requirements.

Another advantage to immunotherapy vs standard chemotherapy has been favorable toxicity rates. PD-L1 inhibitor monotherapy has generally been superior to standard chemotherapy and has been a better option for frail patients. However, the addition of the CTLA-4 inhibitor ipilimumab to PD-L1 blockade has increased the toxicity profile. In this trial, the grade 3 or greater toxicity rate was similar between dual immunotherapy and chemotherapy, although with different major symptoms. In addition, patients with prior autoimmune disease or active brain metastasis were excluded from the study and thus should not be offered dual immunotherapy. A clinician will need to consider if their patient is a candidate for dual immunotherapy before considering the application of this trial.

In the future, researchers will need to compare these agents to the new standard of care. Chemotherapy as a control arm no longer is appropriate in a majority of patients. Some patients in this study were PD-L1 greater than 50% and TMB greater than 10; for them, the control should be pembrolizumab. In addition, sequencing therapy continues to be a challenge. Finally, studies in patients with other malignancies have looked at shorter courses of ipilimumab with reduced toxicity with similar benefit [6], and this could be applied to lung cancer as well.

Application for Clinical Practice

This trial adds an additional actionable target to the array of treatments for NSCLC. In patients with newly diagnosed metastatic non-squamous NSCLC with no actionable EGFR or ALK mutation and PD-L1 less than 50%, testing for TMB on tumor should be performed. If the test shows 10 or greater mutations per megabase, combination nivolumab and ipilimumab should be offered over standard chemotherapy. Special consideration of patient characteristics to determine candidacy and tolerability of this treatment should be evaluated.

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