PET-adapted Anti-PD1 Based First Salvage Therapy For Hodgkin Lymphoma With Nivolumab +/- ICE (NICE)

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INTRODUCTION

Hodgkin Lymphoma is a cancer of the lymphatic system characterized by a neoplasm of lymphoid tissue containing malignant Hodgkin-Reed-Sternberg (HRS) cells. HL is estimated to be diagnosed in 8,800 individuals in 2021 and approximately 960 individuals will die. The 5-year survival rate for HL is 87%. If the cancer is found in its earliest stages, the 5-year survival rate is 91%. Despite the high survival rates approximately 30-40% of patients presenting with HL become refractory to initial therapy or relapse, leaving salvage chemotherapy + autologous hematopoietic cell transplantation as the only potential curative treatment. While this regiment is fairly effective, it is known that there is high toxicity associated with salvage-based chemotherapies. Recent studies have demonstrated that brentuximab vedotin (BV) treatments are highly efficacious and reduce toxicity when combined with salvage chemotherapy, however, due to promising results of the Echelon-1 trial, BV may become part of standard induction therapy. This would make BV potentially unviable as a salvage chemotherapy.

The most traditional course of treatment for an individual with relapsed or refractory HL is ICE (ifosfamide, carboplatin, etoposide) salvage chemotherapy. Studies have demonstrated that ICE is efficacious with an ORR range of 88–100% and CR rate range of 26–67% assessed by PET-CT scan in one study. We seek to combine ICE with Nivolumab as a treatment for relapsed and refractory HL.

Nivolumab (Nivo) is a humanized monoclonal antibody that blocks the interaction between PD-1 and PD-L1. Specifically, nivo binds to the human PD-1 receptor and inhibits the interaction between PD-1 and its ligands PD-L1 and PD-L2. In Hodgkin Lymphoma it is well known that the Reed-Sternberg cells exploit the PD-1 pathway in order to evade immune detection. Alterations in chromosome 9p24.1 found in classic Hodgkin increase the abundance of PD-1 ligands, PD-1 and PD-L2. Therefore, by targeting these pathways it is conceivable that Nivo will prove to be efficacious in treatment of Hodgkin Lymphoma. Currently, nivolumab is approved for the treatment in a variety of solid tumor cancers in multiple countries such as the US, EU, and Japan. As such, safety and toxicity of nivolumab has been thoroughly studied.

The goal of this phase II clinical trial is to evaluate the response patients have to Nivo+ICE therapy in patients not in CR with Nivo alone.

METHODS

This was a multi-center phase II clinical trial that implements a Simon Two-Stage Optimal Design to evaluate the anti-lymphoma activity of NIVO±ICE chemotherapy. A maximum of 43 participants are expected to be enrolled using a rate of 0.05 and power of 80% a type I error to create a sample size based on the desire to discriminate between a promising CR rate of 70% from a disappointing CR rate of 50% (a rate below what current therapies can achieve).

Eligible patients were 18 years or older who weighed more than 59 kilograms. Patients were required to have histologically confirmed CD30+ HL that had relapsed or was refractory to initial treatment. Additionally, patients could only have received first line chemotherapy, with prior consolidative radiation therapy allowed. ECOG performance status must be between 0-2 inclusive and patients must have adequate organ and marrow function.

Patients received 240 mg nivolumab over approximately 30 minutes every 2 week for 3 cycles administered IV. After the first 6 weeks of treatment, PET-CT was performed and the results determined subsequent treatment. Patients in complete response (CR) or partial response (PRR) received another 3 cycles/6weeks of nivo for a total of 6 cycles/12 weeks followed by another PET-CT. Patients in CR after 6 cycles/12 weeks of nivolumab proceeded to AHCT. Patients who had progressive disease (PD) after 3 cycles/6 weeks or 6 cycles/12 weeks of nivolumab proceeded to receive 2 cycles (21 days/cycle) of nivolumab plus ICE (NICE): nivolumab 240mg day 1, etoposide 100 mg/m2 IV on Days 1-3, carboplatin AUC 5 (750 mg maximum) IV on Day 2, ifosfamide IV on Day 2 5000 mg/m2. Patients with stable disease (SD) after 3 cycles/6 weeks could proceed with an additional 3 cycles/6 weeks of nivolumab or proceed to NICE at the discretion of the treating investigator. Patients with SD after 6 cycles/12 weeks of nivolumab received NICE. Following NICE, patients in PR or CR could proceed to autologous hematopoietic stem cell transplantation (AHCT), while patients with SD or PD were removed from the study.

The primary endpoints of the study were CR rate at the completion of the NIVO ± ICE regimen, and toxicity in the safety monitoring segment of the study. Secondary endpoints included estimates of overall response rate, response duration, overall and event-free survival, CD34+ yield, proportion of patients who collected ≥2 x106 CD34+ cells/kg. For patients who underwent AHCT, time to engraftment, non-relapse mortality and relapse-progression incidence were further secondary endpoints.

RESULTS

Forty-three patients were enrolled and participated in the study. Twenty-six patients were male (60%) and the median age was 35 years (range, 18-70). At baseline, twenty-five patients (58%) had advanced stage cancer, sixteen patients had B symptoms (37%), and eighteen patients had bulky disease at baseline (42%).

All 43 patients were evaluable for safety and 41 had a response assessment and were evaluable for efficacy. Thirty-nine patients completed nivolumab monotherapy and 4 patients discontinued prior to completing nivolumab monotherapy. Three patients discontinued due to toxicity during nivolumab monotherapy (1 patient with grade 4 encephalitis, 1 patient with grade 2 pneumonitis, one with Gr 2 thyroiditis in CR after 2 cycles and proceeded to AHCT) and 1 patient died of sepsis due to an untreated dental abscess during nivolumab monotherapy that was unrelated to study treatment. One patient withdrew consent after completing nivo monotherapy (refused NICE). 9 patients proceeded to receive NICE. In total, 38 (88%) patients completed all intended protocol therapy.

Of the 41 evaluable patients, the objective response rate (ORR) and CR after 3 cycles of nivo were 97% (37/41), respectively. Thirty-seven patients proceeded to receive 3 additional cycles of nivo, and the ORR and CR after 6 cycles were 89% (33/37) and 78% (29/37), respectively. The end of nivo ORR and CR rate among all 41 evaluable patients were 83% (34/41) and 73% (30/41), respectively. Among the 9 patients who received NICE, all 9 (100%) responded with 8 (89%) achieving CR. At the end of all protocol therapy (Nivo or Nivo/NICE), the ORR and CR rates were 95% (39/41) and 93% (38/41), respectively, among evaluable patients, and 91% and 88% among all-treated patients. Response rates were similar in patients with primary refractory and relapsed cHL.

DISCUSSION

PET-adapted Anti-PD1 based first salvage therapy for Hodgkin Lymphoma with NIVO±ICE was well tolerable and effective, resulting in a high CR rate and bridged most patients to transplant without traditional chemotherapy. Patients who received nivolumab and then proceeded directly to AHCT in response had few relapses and excellent post-AHCT outcomes suggesting that PD-1 blockade alone can serve as an effective bridge to AHCT independent of BV. CR rate using nivolumbal as a first salvage therapy was unexpectedly high at 70%, meaning few patients were treated using NIVO±ICE therapy. Of the few patients that did receive sequential NICE, CR rate was high in patients not in CR after nivo monotherapy and NICE appeared to be safe after second-line nivo with no unexpected safety signals. Stem cell mobilization and collection was adequate following nivo or sequential nivo/NICE and there were no concerning safety signals after AHCT in this cohort of anti-PD1 treated patients.

Due to such a high number of patients put into CR with nivo monotherapy alone, very few patients received NIVO±ICE therapy, which was what the trial initially sought to study. As such, a second cohort, Cohort B, will need to be gathered in order to further study the efficacy of NIVO±ICE therapy in patients with refractory/relaped cHL.

In conclusion, PET-adapted sequential nivolumab/NICE salvage therapy was a safe and effective bridge to AHCT that resulted in a high rate of durable remissions in patients who proceeded to AHCT. These findings along with the promising results observed in other studies incorporating PD-1 blockade into salvage therapy for cHL suggest that a randomized comparison of conventional versus anti-PD1-based salvage therapy should be performed.