Does the Poly (ADP-Ribose) Polymerase Inhibitor Veliparib Merit Further Study for Cancer-Associated Weight Loss? Observations and Conclusions from Sixty Prospectively Treated Patients

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Abstract

Background: More than 80% of patients with advanced cancer develop weight loss. Because preclinical data suggest poly (ADP-ribose) polymerase (PARP) inhibitors can treat this weight loss, this study was undertaken to explore the PARP inhibitor veliparib for this indication.

Objective: The current study was undertaken to analyze prospectively gathered data on weight in cancer patients on PARP inhibitors.

Design/Setting: The current study relied on a previously published, prospectively conducted phase 1 single institution trial that combined veliparib and topotecan (NCT01012817) as antineoplastic therapy for advanced cancer patients. Serial weight data and, when available and clinically relevant, computerized tomography scans were also examined.

Measurements: The primary endpoint was 10% or greater weight gain from trial enrollment.

Results: Nearly all 60 patients lost weight over time. Only one patient manifested a 10% or greater gain in weight. However, review of computerized tomography L3 images showed this weight gain was a manifestation of ascites. Four other patients gained 5% of their baseline weight. However, findings in two patients with available radiographs showed no evidence of muscle augmentation.

Conclusions: The addition of the PARP inhibitor veliparib to chemotherapy does not appear to result in notable weight gain or in weight maintenance in patients with advanced cancer. Interventions other than PARP inhibitors should be considered for the palliation/treatment of cancer-associated weight loss.

Keywords: cachexia; cancer; veliparib; weight loss

Introduction

MORE THAN 80% OF PATIENTS with advanced cancer develop cancer-associated weight loss, a syndrome characterized by a forfeiture of muscle and a decline in functional status, quality of life, and survival.^{1,2} Treating or palliating this syndrome has been unsuccessful. Enobosarm and anamorelin were tested in large, multicenter trials that accrued hundreds of patients—only to fall short of achieving their primary endpoints.^{3,4} Such findings underscore the current therapeutic void for metastatic cancer patients who suffer from this syndrome and point out the need to continue

to investigate agents that hold promise in improving muscle and its functionality with the goal of improving patients' quality of life and survival.

Inhibitors of poly (ADP-ribose) polymerase (PARP) have received Food and Drug Administration (FDA) approval as antineoplastic agents. Interestingly, however, >20 years of preclinical data also suggest that, despite the purported effects of this class of agents on fat, these agents are able to treat muscle loss.^{5–19} This salutary effect on muscle could lead to weight gain. Genetic and pharmacological inhibition of PARP-1 in mouse models demonstrate enhanced muscle fitness as a result of increased mitochondrial function.^{20,21} Mice

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treated with PARP inhibitors show an increased abundance of mitochondrial respiratory complexes as well as increased mitochondrial respiratory capacity.²⁰ Mice with a *PARP-1* deletion demonstrate greater mitochondrial content and increased energy expenditure in brown adipose and skeletal muscle as well as protection against metabolic disease.²² PARP inhibition also increases NAD (+) content and SIRT1 activity, resulting in enhanced oxidative phosphorylation and providing a possible mechanism for enhanced metabolism in skeletal muscle.^{22–24} Furthermore, mouse models of reperfusion injury and aging reveal preservation of skeletal muscle mitochondrial biogenesis and bioenergetics with PARP inhibitors.^{21,24} The putatively protective role of PARP inhibitors may, in part, reside in their apparent antioxidant capacity, as demonstrated in cultured mouse and rat myoblast cell line (C2C12 and L6, respectively) treated with the PARP inhibitor PJ34.²³ Moreover, PARP inhibitors (3-aminobenzamide, PD128763) have no adverse effect on fusion of L6 myoblasts, a finding that suggests these agents attenuate factors that contribute to muscle atrophy.²³ Such data—in conjunction with several other preclinical studies in cancer and noncancer settings and in conjunction with a clear absence of prior, relevant clinical data—underscore the need to study PARP inhibitors clinically for cancer-associated weight loss.^{25–33}

Methods

Overview

The current study relied on a previously published phase 1 trial that combined veliparib and topotecan (NCT01012817) for cancer treatment.³⁴ This parent trial served as the platform for the investigation reported here. This parent trial sought to determine the maximally tolerated dose of this drug combination and, therefore, tested a wide range of veliparib doses from 10 mg/day in 3 day treatment intervals on a weekly basis up to 300 mg twice a day administered at these same intervals in combination with weekly chemotherapy.

Eligibility

For the current study, all patients who were enrolled in the parent trial and who had weight data were included. Eligibility criteria appear on www.clinicaltrials.gov as well as in the published article.³⁴ In brief, eligible patients had an incurable malignancy; no more than two prior types of chemotherapy (at the lower doses of veliparib; patients were allowed to have had more prior chemotherapy exposure); evidence of acceptable hepatic, renal, and bone marrow function; and an anticipated life expectancy of at least three months.

Acquisition and evaluation of data

Serial weights at four-week intervals were abstracted from each patient's clinical record and are presented as percentage change from baseline over time. Medical records were reviewed for weight loss of 10 pounds or more in the three months before trial enrollment.

The primary goal of this study was to report the number of patients who manifested a 10% or greater weight gain from trial enrollment. This 10% threshold was chosen because (1) prior studies for cancer-associated weight loss had used this threshold to define success, (2) preclinical data that reported weight data used this threshold, and (3) conversely, >10%

weight loss is deemed a clinical marker of severe malnutrition.^{35–39} This study focused on weight as the primary endpoint because it was assessed consistently and frequently, more so than computerized tomography scans, and because the parent study had a high patient dropout rate (median number of chemotherapy cycles of two), a situation that would have lessened power and potentially biased conclusions in favor of fitter patients.⁴⁰

The parent trial mandated computerized tomography scans at eight-week intervals while patients remained on therapy. For the current study, when available and clinically relevant, computerized tomography scans were visually inspected at the L3 level (and at other levels when appropriate) to further assess patients who had gained weight to characterize whether muscle augmentation explained any observed weight gain.^{41,42}

Results

Demographics

All patients who had enrolled in the original trial are included in these analyses, with the exception of two who had no weight data. Table 1 shows baseline demographics, which are most notable for gender and tumor type imbalances, both of which appear reflective of and driven by PARP inhibitor development plans. Also of note, only 10% of patients had lost weight in the three months before trial enrollment.

Weight data

Nearly all patients lost weight over time (Fig. 1). No weight trends were apparent based on dose of veliparib.

Only one patient with ovarian cancer manifested a 10% or greater gain in weight. However, her computerized tomography image at the L3 cross section showed this weight gain was a manifestation of ascites (Fig. 2). Four other patients gained 5% of their baseline weight; this weight gain was relatively transient in two patients and occurred before scan obtainment. In the other two patients with 5% weight gain, no evidence of muscle augmentation was observed with inspection of sequential computerized tomography scans.

TABLE 1. DEMOGRAPHICS (N=60)

<i>Median age (range)^a</i>	57 (34,78)
Sex	
Male	1 (2)
Female	59 (98)
Cancer type	
Ovarian ^b	53 (88)
Endometrial	4 (7)
Cervical	1 (2)
Lung	1 (2)
Weight loss at trial entry?	
Yes	6 (10)
No	41 (68)
Unknown	13(22)

^aNumbers in parentheses are percentages of the entire cohort unless otherwise noted.

^bIncludes ovarian, fallopian tube, and primary peritoneal cancer.

FIG. 1. Most patients lost weight after trial enrollment. Only one patient manifested a 10% or greater gain of her baseline weight.

FIG. 2. Serial computerized tomography scans at the L3 vertebra (top image at trial entry and bottom at trial discontinuation) show no evidence of incremental muscle gain. Instead, the bottom image shows notable ascites, which accounted for the observed weight gain, and evidence of muscle thinning.

Tumor response data and adverse events

As previously reported, a partial or complete tumor response was observed in five patients. Adverse events are described in detail in the article for the parent trial but are in keeping with what has been previously described with PARP inhibitors; hematologic toxicity, as manifested with myelosuppression, was most commonly observed.

Discussion

Despite a strong preclinical rationale for testing PARP inhibitors for the treatment of cancer-associated weight loss, this study found no apparent clinical benefit with respect to weight gain or stabilization with veliparib. Even lowering the threshold for clinically favorable weight gain to 5% from trial enrollment showed no apparent increase in lean tissue on computerized tomography scans. Our findings suggest that future clinical trials aimed at treating cancer-associated weight loss should focus on interventions other than PARP inhibitors.

No previous studies have examined PARP inhibitors for cancer-associated weight loss, making this study novel despite its negative conclusions. In contrast, prior studies had focused mostly on muscle diseases of other etiologies.^{20–27} However, the findings reported here should not detract from examining PARP inhibitors for muscle loss from other non-cancer etiologies.

This study has two limitations. First, one might criticize the fact that a PARP was combined with chemotherapy. This approach can be justified because (1) no previous clinical studies suggest topotecan would detract from veliparib's purported salutary muscle effects, (2) prior studies have shown successful chemotherapy leads to weight gain, and (3) precedent exists for including chemotherapy in cancer-associated weight loss trials.^{3,4,35,36} With respect to this first point, a handful of studies have suggested that topotecan might have negative effects on smooth muscle, an observation that suggests that there might still be opportunity to study PARP inhibitors for the treatment of cancer-associated muscle loss in conjunction with different drug combinations.^{9–11} With respect to this last point, antineoplastic therapy is a critical component of cancer care and must be integrated into cancer-associated weight loss trials.^{3,4,35,36} Second, we had no placebo arm to benchmark weight outcomes. However, because we saw a decline in weight over time in nearly all patients, these findings are compelling.

This study also has strengths. First, this sample size of 60 patients provides a robust descriptive study. Our observations relevant to weight gain were complemented by inspection of computerized tomography scans that provide rigor to substantiate these negative findings. Second, previous investigators have commented on the fact that when cancer patients begin to lose weight, the ability to stop that weight loss appears limited.⁴³ Thus, the fact that weight loss was not an eligibility criterion for the parent trial coupled with the fact that only 10% of patients had baseline weight loss provided an evenhanded opportunity for veliparib to work. Thus, the negative findings here remain noteworthy.

Finally, our study design is another strength. The negative phase III trials with enobosarm and anamorelin cost millions of dollars.^{3,4} Reanalyzing data from a previous trial with a different primary endpoint—and bypassing the time and

expense of a prospective trial—has merit. Our negative findings encourage investigators to refocus on more promising areas of investigation for cancer-associated weight loss.

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Author Disclosure Statement

No competing financial interests exist.

References

- Carr RM, Enriquez-Hesles E, Olson RLO, et al.: Epigenetics of cancer-associated muscle catabolism. *Epigenomics* 2017. [Epub ahead of print.]
- Martin L, Birdsell L, Macdonald N, et al.: Cancer cachexia in the age of obesity: Skeletal muscle depletion is a powerful prognostic factor, independent of body mass index. *J Clin Oncol* 2013;31:1539–1547.
- Temel JS, Abernethy AP, Curott DC, et al.: Anamorelin in patients with non-small cell lung cancer and cachexia: Results of two randomized, double-blind phase 3 trials. *Lancet Oncol* 2016;17:519–531.
- <https://www.thepharmaletter.com/article/enobosarm-fails-endpoints-in-ph-iii-study> (Last accessed November 23, 2017).
- Kir S, Spiegelman BM: Cachexia & brown fat: A burning issue in cancer. *Trends Cancer* 2016;2:461–463.
- Petrucelli M, Schweiger M, Schreiber R, et al.: A switch from white to brown fat increases energy expenditure in cancer-associated cachexia. *Cell Metab* 2014;20:433–447.
- Beijer E, Schoenmakers J, Vijgen G, et al.: A role of active brown adipose tissue in cancer cachexia? *Oncol Rev* 2012;6:e11.
- Edstrom S, Kindblom LG, Lindmark L, Lundholm K: Metabolic and morphologic changes in brown adipose tissue from non-growing mice with an isogeneic sarcoma. Evaluation with respect to development of cachexia. *Int J Cancer* 1986;37:753–760.
- Parry TJ, Thyagarajan R, Argentieri D, et al.: Effects of drug combinations on smooth muscle cell proliferation: An isobolographic analysis. *Eur J Pharmacol* 2006;532:38–43.
- Brehm BR, Bock C, Wesselborg S, et al.: Prevention of human smooth muscle cell proliferation without induction of apoptosis by the topoisomerase I inhibitor topotecan. *Biochem Pharmacol* 2001;61:119–127.
- de la Loza MC, Wellinger RE: A novel approach for organelle-specific DNA damage targeting reveals different susceptibility of mitochondrial DNA to the anticancer drugs camptothecin and topotecan. *Nucleic Acids Res* 2009;37:e26.
- Vaitek JA, Celi FS: The role of adipose tissue in cancer-associated cachexia. *Exp Biol Med* (Maywood) 2017;242:473–481.
- Tsoli M, Swarbrick MM, Robertson GR: Lipolytic and thermogenic depletion of adipose tissue in cancer cachexia. *Semin Cell Dev Biol* 2016;54:68–81.
- Sinha G: Homing in on the fat and cancer connection. *J Natl Cancer Inst* 2012;104:966–967.
- Rousseau C, Bourbouloux E, Campion L, et al.: Brown fat in breast cancer patients: Analysis of serial (18)F-FDG PET/CT scans. *Eur J Nucl Med Mol Imaging* 2006;33:785–791.
- Huang YC, Chen TB, Hsu CC, et al.: The relationship between brown adipose tissue activity and neoplastic status: An (18)F-FDG PET/CT study in the tropics. *Lipids Health Dis* 2011;10:238.
- Gnanaswaran S, Tandy B, Fulham MJ: Brown fat FDG uptake abolished by radiotherapy. *Clin Nucl Med* 2015;40:437–438.
- Dizon QS, Southam CM: Growth of human cancer cells in interscapular brown fat of rats. *Transplantation* 1968;6:351–357.
- Cronin CG, Prakash P, Daniels GH, et al.: Brown fat at PET/CT: Correlation with patient characteristics. *Radiology* 2012;263:836–842.
- Pirinen E, Canto C, Jo YS, et al.: Pharmacological inhibition of poly(ADP-ribose) polymerases improves fitness and mitochondrial function in skeletal muscle. *Cell Metab* 2014;19:1034–1041.
- Conrad MF, Albadawi H, Stone DH, et al.: Local administration of the poly ADP-ribose polymerase (PARP) inhibitor PJ34 during hindlimb ischemia modulates skeletal muscle reperfusion injury. *J Surg Res* 2006;135:233–237.
- Bai P, Canto C, Oudart H, et al.: PARP-1 inhibition increases mitochondrial metabolism through SIRT1 activation. *Cell Metab* 2011;13:461–468.
- Olah G, Szczesny B, Brunyaszki A, et al.: Differentiation-associated downregulation of poly(ADP-ribose) polymerase-1 expression in myoblasts serves to increase their resistance to oxidative stress. *PLoS One* 2015;10:134227.
- Mohamed JS, Wilson JC, Myers MJ, et al.: Dysregulation of SIRT-1 in aging mice increases skeletal muscle fatigue by a PARP-1-dependent mechanism. *Aging (Albany NY)* 2014;6:820–834.
- Halmosi R, Berente Z, Osz E, et al.: Effect of poly(ADP-ribose) polymerase inhibitors on the ischemia-reperfusion-induced oxidative cell damage and mitochondrial metabolism of Langendorff heart perfusion system. *Mol Pharmacol* 2001;59:1497–1505.
- Hua HT, Albadawi H, Entabi F, et al.: Polyadenosine diphosphate-ribose polymerase inhibition modulates skeletal muscle injury following ischemia reperfusion. *Arch Surg* 2005;140:344–351.
- Palfi A, Toth A, Hanto K, et al.: PARP inhibition prevents postinfarction myocardial remodeling and heart failure via the protein kinase C/glycogen synthase kinase 3 β pathway. *J Mol Cell Cardiol* 2006;41:149–159.
- Butler A, Ordahl CP: Poly(ADP-ribose) polymerase binds with transcription enhancer factor 1 to MCAT1 elements to regulate muscle-specific transcription. *Mol Cell Biol* 1999;19:296–306.
- Chacon-Cabrera A, Mateu-Jimenez M, Langohr K, et al.: Role of PARP activity in lung cancer-induced cachexia: Effects on muscle oxidative stress, proteolysis, anabolic markers, and phenotype. *J Cell Physiol* 2017;232:3744–3761.
- Hu B, Wu Z, Hergert P, et al.: Regulation of myofibroblast differentiation by poly(ADP-ribose) polymerase 1. *Am J Pathol* 2013;182:71–83.
- Long CA, Boulom V, Albadawi H, et al.: Poly-ADP-ribose-polymerase inhibition ameliorates hind limb perfusion ischemia reperfusion injury in a murine model of type 2 diabetes. *Ann Surg* 2013;258:1087–1095.
- Belizario JE, Lorite MJ, Tisdale MJ: Cleavage of caspases -1, -3, -6, -8, and -9 substrates by proteases in skeletal muscles from mice undergoing cancer cachexia. *Br J Cancer* 2001;84:1135–1140.

33. Ledermann JA, Harter P, Gourley C, et al.: Quality of life during olaparib maintenance therapy in platinum-sensitive relapsed serous ovarian cancer. *Br J Cancer* 2016;115: 1313–1320.
34. Wahner Hendrickson AE, Menefee ME, Hartmann LC, et al.: A phase 1 clinical trial of the poly(ADP-ribose) polymerase inhibitor veliparib and weekly topotecan in patients with solid tumors. *Clin Cancer Res* 2018;24:744–752.
35. Jatoi A, Rowland K, Loprinzi CL, et al.: An eicosapentaenoic acid supplement versus megestrol acetate versus both for patients with cancer-associated wasting: A North Central Cancer Treatment Group and National Cancer Institute of Canada collaborative effort. *J Clin Oncol* 2004;22: 2469–2476.
36. Jatoi A, Windschitl HE, Loprinzi CL, et al.: Dronabinol versus megestrol acetate versus combination therapy for cancer-associated anorexia. *J Clin Oncol* 2002;20:567–573.
37. Muscaritoli M, Lucia S, Farcomeni A, et al.: Prevalence of malnutrition in patients at first medical oncology visit; the PreMiO study. *Oncotarget* 2017;8:79884–79896.
38. Harvey SE, Parrott F, Harrison DA, et al.: Trial of the route of early nutritional support in critically ill adults. *N Engl J Med* 2014;371:1673–1684.
39. Collins N: Protein-energy malnutrition and involuntary weight loss: Nutritional and pharmacological strategies to enhance wound healing. *Exper Opin Pharmacother* 2003;4: 1121–1140.
40. Le-Rademacher JG, Crawford J, Evans WJ, Jatoi A: Overcoming obstacles in the design of cancer anorexia/weight loss trials. *Crit Rev Oncol Hematol* 2017;117:30–37.
41. Prado CM, Baracos VE, Xiao J, et al.: The association between body composition and toxicities from the combination of doxil and trabectedin in patients with advanced relapsed ovarian cancer. *Appl Physiol Nutr Metab* 2014;39: 693–698.
42. Holt DQ, Strauss BJ, Lau KK, Moore GT: Body composition analysis using abdominal scans from routine clinical care in patients with Crohn's disease. *Scan J Gastroenterol* 2016;51:842–847.
43. Fearon K, Arends J, Baracos V: Understanding the mechanisms and treatment options of cancer cachexia. *Nat Rev Clin Oncol* 2013;10:90–99.

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