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In vivo Anti-Cancer Activity of a Liposomal Nanoparticle Construct of Multifunctional Tyrosine Kinase Inhibitor 4-(4'-Hydroxyphenyl)-Amino-6,7-Dimethoxyquinazoline

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Abstract

The quinazoline derivative 4-(4'-hydroxyphenyl)-amino-6,7-dimethoxyquinazoline (WHI-P131/JANEX-1; CAS 202475-60-3) is a dual-function inhibitor of Janus kinase 3 (JAK3) and Epidermal Growth Factor (EGF) receptor kinase. A PEGylated liposomal nanoparticle formulation of GMP-grade WHI-P131 exhibited potent in vivo activity against breast cancer cells. Notably, this therapeutic nanoparticle formulation of GMP-grade WHI-P131 was substantially more effective than the standard chemotherapy drugs paclitaxel, gemcitabine, and gefitinib against chemotherapy-resistant breast cancer in the MMTV/*Neu* transgenic mouse model. These experimental results demonstrate that the nanotechnology-enabled delivery of WHI-P131 shows therapeutic potential against breast cancer.

Keywords: CAS 202475-60-3; JAK3; Quinazoline; GMP; WHI-P131; Breast cancer

Introduction

WHI-P131 is a dual-function inhibitor of JAK3 and EGF receptor tyrosine kinases [20]. It is being developed as a potential anti-cancer and immunomodulatory drug candidate [28,26]. WHI-P131 demonstrated potent *in vivo* anti-inflammatory and immunomodulatory activity in several preclinical animal models [3-7,13,14,26]. It has been shown that WHI-P131 exhibits potent pro-apoptotic anti-cancer activity against human cancer cells with constitutive JAK3/STAT3 activation [1,2,11,12,15,16,19,20] and displays chemopreventive properties in animal models of gastrointestinal neoplasia [25] and non-melanoma skin cancer [21]. WHI-P131 exhibited a favorable pharmacokinetics and safety profile in preclinical studies in rodents and monkeys [24]. Forty-eight distinct therapeutic liposomal nanoparticle constructs of WHI-P131 have been prepared and a PEGylated lead formulation (viz.: WHI-P131 [NP]) showed significant *in vitro* cytotoxicity against primary human leukemia cells from B-lineage acute lymphoblastic leukemia (ALL) and chronic lymphocytic leukemia (CLL) patients as well as potent *in vivo* anti-leukemic activity in a SCID mouse xenograft model of highly aggressive and radiochemotherapy resistant ALL [23]. WHI-P131 [NP] was substantially more potent *in vivo* than non-encapsulated WHI-P131 and drug-free nanoparticles exhibited no anti-cancer activity in the SCID mouse xenograft model [23]. The purpose of the present study was to further evaluate the therapeutic potential of WHI-P131 [NP] against chemotherapy-resistant breast cancer in the MMTV/*Neu* transgenic mouse model of metastatic ErbB2/HER2$^+$ breast cancer. In MMTV/*Neu* transgenic mice, the expression of wild-type rat *Her2/neu* gene is forced in the mammary gland under the control of the MMTV long terminal repeat. *Neu* transgenic mice develop rapidly progressive and metastatic breast cancer [22,27]. WHI-P131 [NP] was substantially more potent than the standard chemotherapy drugs paclitaxel, gemcitabine, and gefitinib at clinically applicable or higher dose levels and resulted in shrinkage of both primary and metastatic tumors in MMTV/Neu transgenic mice. These experimental results demonstrate that the nanotechnology-enabled delivery of WHI-P131 shows therapeutic potential against breast cancer.

Materials and Methods

Preparation of WHI-P131 [NP]

A PEGylated liposomal nanoparticle (NP) formulation of GMP-grade WHI-P131 (Encapsulated WHI-P131 concentration: 30.1±0.8 mg/mL; Approximate particle size after extrusion: 100 nm) was prepared using lipid film hydration, as described [23]. The liposome bilayer membranes of the nanoparticles were composed of dipalmitoylphosphatidylcholine (DPPC) and cholesterol [23]. Polyethylene glycol (PEG)-derivatized lipid 1,2-distearoyl-*sn*-glycero-3-phosphoethanolamine-*n*-[poly(ethylene glycol) 2000] (DSPE-PEG_{2000}) was also incorporated into the membranes for the purpose of enhanced steric stabilization [23].

Animals

We used the well established transgenic mouse model of ErbB2/HER-2$^+$ chemotherapy-resistant breast cancer [22,27]. MMTV/*Neu* mice [FVB/N-TgN (MMTV neu) 202MUL; Jackson Laboratory, Bar Harbor, Maine] [22,27] were bred to produce multiple litters. All mice were housed in microisolator cages (Lab Products, Inc., Maywood, NY, USA) containing autoclaved bedding in a controlled specific pathogen-free (SPF) environment (12-h light/12-h dark photoperiod, 22±1°C, 60±10% relative humidity), which is fully accredited by the USDA (United States Department of Agriculture). Animal studies were approved by Parker Hughes Institute Animal Care and Use Committee and all animal care procedures conformed

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to the Guide for the Care and Use of Laboratory Animals (National Research Council, National Academy Press, Washington DC 1996, USA).

Treatment of MMTV/*Neu* mice

Animals carrying one or more tumors were randomly placed in the study. Tumor-bearing mice were randomly assigned to PBS, WHI-P131-free vehicle, NP formulation of GMP-grade WHI-P131, paclitaxel (Taxol), gemcitabine (Gemzar) or gefinitib (Iressa) treatment groups. Chemotherapeutic drugs were obtained from the Parker Hughes Cancer Center Pharmacy (50 mg/kg, N= 9; 100 mg/kg, N= 9; 150 mg/kg, N= 8). WHI-P131 [NP] (50 mg/kg, N= 9; 100 mg/kg, N= 9; 150 mg/kg, N= 8) was administered by daily intraperitoneal injections on 5 consecutive days per week. Paclitaxel/Taxol (N= 27) was administered intraperitoneally on days 1, 3, and 5 of each week at a dose level of 6.7 mg/kg. Gemcitabine (N= 34) was administered on days 1 and 8 at a dose level of 33.7 mg/kg. Gefinitib (N= 20) was suspended in distilled water and administered at 75 mg/kg dose in 0.2 ml by gastric gavage with a 20-gauge gavage needle. Control group (N= 38) included mice that were treated daily for 5 days/week with ip injections of WHI-P131-free vehicle (n= 9), WHI-P131 [NP] at the suboptimal 50 mg/kg dose level (N= 9) or PBS (N= 20). Tumor growth was determined by the measurement of tumors with a caliper in three dimensions three days a week and expressed as tumor volume in cubic millimeters (mm3). Tumor volumes were calculated using the formula for the volume of a prolate spheroid, V= 4/3 x 3.14 x length/2 x width/2 x depth/2. Tumor size for each tumor was normalized to the starting volume for that particular tumor.

Statistical analysis

Tumor volume measurements were taken at day 1, 7 and 14 for control mice and those treated with WHI-P131 [NP], Gefinitib, Gemcitabine and Taxol. To investigate the treatment effect on the growth of tumors across 7 and 14 days we used an ANOVA model that accounted for variance components between mice and between initial tumor volumes at day 1. To control for mouse to mouse differences a random effect was included in the model using the REML method (Restricted or residual maximum Likelihood) for determining the variance component of this effect. Considerable variation was observed in tumor volumes at day 1 of the experiment, therefore, to assess the effect of tumor volume at day 1 and subsequent growth of tumors at days 7 and 14, the day 1 volume was included as a co-variate for the ANOVA models performed at days 7 and 14. A second interaction co-variate in the model controlled for differences in tumor volumes that were dependent on treatment (Day1*treatment interaction). These three control factors enabled testing of differences in tumor growth that accounted for mouse differences, multiple measurements taken from a mouse and tumor volume differences to follow growth over 14 days. We examined the distribution of the residuals of the model for equal dispersion around the line of best fit. We normalized all tumor volumes to day 1 measurements and investigated the specific treatment effect on the growth of tumors across 7 and 14 days using Student's T-tests (2-tailed, corrected for unequal variances; Excel formula). P-values less than 0.05 were deemed significant without correction for multiple comparisons as the True Discovery Rate calculated for all the tests performed exceeded 90%. The PBS, vehicle, and low dose WHI-P131 [NP] groups were combined into a single control group. We performed the following comparisons: Control vs. WHI-P131 [NP]; control versus Gefinitib, Gemcitabine and Taxol; WHI-P131 [NP] versus Gefinitib, Gemcitabine and Taxol. Two sets of T-tests were performed at 7 and 14 days.

Results

We examined the *in vivo* anti-cancer activity of the NP formulation of GMP-grade WHI-P131 in the MMTV/*Neu* transgenic mouse model of $HER2^+$ metastatic breast cancer. At a 50 mg/kg dose level, WHI-P131[NP] (like WHI-P131-free vehicle or PBS) did not exhibit significant *in vivo* anti-tumor activity capable of preventing tumor progression. However, at 100-150 mg/kg dose levels, WHI-P131 [NP] caused tumor shrinkage (Figure 1) and prevented the tumor growth. We applied an ANOVA model to compare the overall effect of control and drug treatments showing that 86% of the variation in tumor volumes was explained by the model at day 7 ($P<0.0001$) with a significant effect of treatment ($F_{4,134}= 7.813$, $P<0.0001$) taking into account the effect of differences in tumor volumes at day 1 ($F_{1,209}= 388$, $P<0.0001$). Examination of the ANOVA model at 14 days showed that 64% of the variation was explained ($P<0.0001$) with significant effects of treatment ($F_{4,164}= 9.755$, $P<0.0001$), day 1 volume ($F_{1,208}= 141$, $P<0.0001$) and day1*treatment interaction ($F_{4,205}= 3.509$, $P= 0.009$). Since there were significant effects for day 1 tumor volumes for both 7 and 14 day treatments and significant treatment effects accounting for these observed differences in day 1 measurements, we normalized all tumor volumes to day 1 measurements for statistical comparisons using T-tests of specific treatment groups. Specific comparisons of WHI-P131 [NP] with other drug treatments showed that it was significantly more effective than paclitaxel, gemcitabine, or gefitinib at the applied dose levels and treatment schedules ($p<0.0001$ for all comparisons), as documented by the significantly smaller day 7 and day 14 normalized tumor volumes

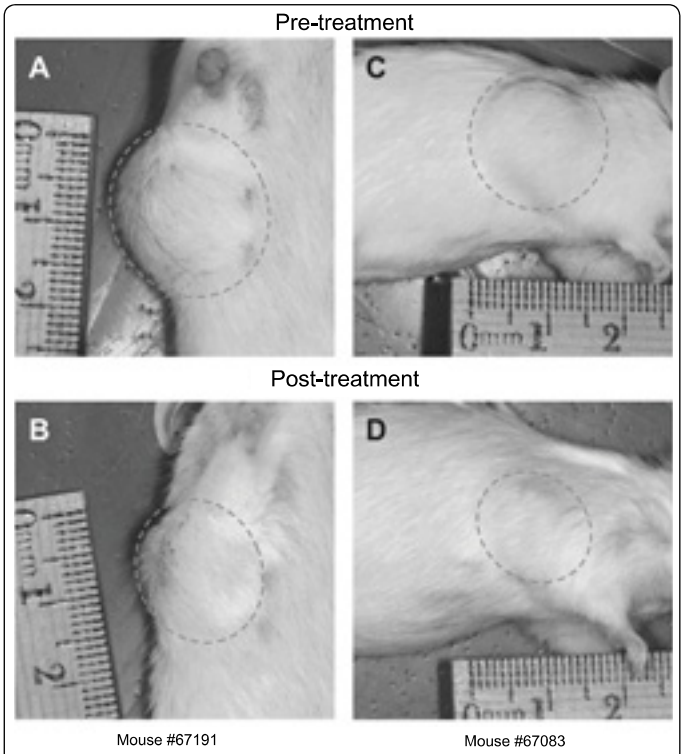

Figure 1: Effect of Nanoparticle Formulation of GMP-grade WHI-P131 on the Growth of Mammary Tumors in MMTV/*Neu* Transgenic Mice. WHI-P131 [NP] (100 mg/kg) treatment resulted in significant tumor regression within 2 weeks in the depicted tumors of mouse # 67191 (***A and B***) and # 67083 (***C and D***). Normalized post-treatment tumor volumes were 0.32 (Day 1 volume = 1726 mm^3, Day 14 volume = 546 mm^3) for mouse # 67191 and 0.35 (Day 1 volume = 837 mm^3, Day 14 volume = 291 mm^3) for mouse #67083.

in the WHI-P131 [NP] treatment group compared to other groups (Figure 2, Table 1). As shown in Figure 2 and Table 1, there was a significant decrease in tumor volume and arrest of tumor growth for WHI-P131[NP] treated mice (normalized volumes: 0.77±0.04 on day 7, P= $7.5x10^{-9}$ and 0.70±0.06, on day 14, P= $1.5x10^{-7}$ and continuation of growth for the other three drug treatments. While the tumor sizes consistently increased between days 7 and 14 for control mice, tumor shrinkage was observed in some of the WHI-P131 [NP] treated mice (Figure 2). It is noteworthy that the initial tumor volumes in the WHI-P131 [NP] treated test group were significantly larger than in the control group or chemotherapy group (1004±98 mm^3 vs. 675±60 mm^3 (Control) and 518±32 mm^3 (Chemotherapy) (Table 1). Taken together, these results illustrate that GMP-grade WHI-P131 has promising *in vivo* anti-cancer activity in this chemotherapy-resistant breast cancer model when used as a nanoparticle formulation.

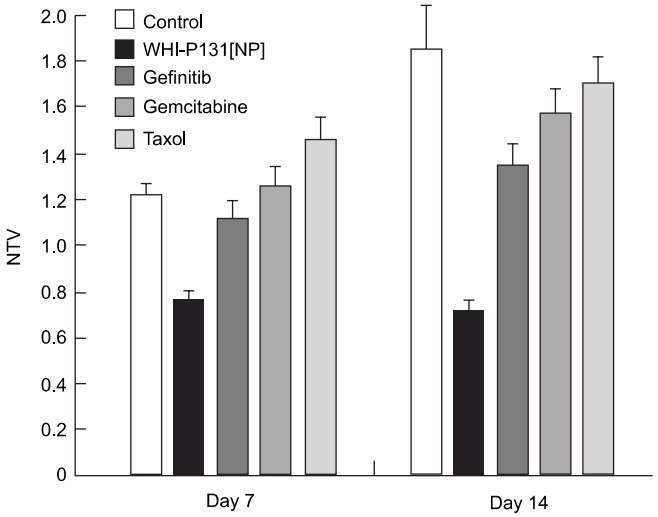

Figure 2: Anti-Tumor Activity of A Nanoparticle Formulation of GMP-grade WHI-P131 in the MMTV/*Neu* Transgenic Mouse Model of Chemotherapy-Resistant Breast Cancer. Tumor growth was determined by the measurement of tumors with a caliper in three dimensions three days a week and expressed as tumor volume in cubic millimeters (mm^3). Tumor volumes were calculated using the formula for the volume of a prolate spheroid, V= 4/3 x 3.14 x length/2 x width/2 x depth/2. WHI-P131 [NP] was administered by daily intraperitoneal injections on 5 consecutive days per week. Tumor growth for each mouse was normalized to the starting volume for that particular tumor on day 1 of detection. Therefore, each mouse also served as its own control. The mean and standard error of mean for the normalized tumor volumes (NTV) are depicted for 38 control mice (PBS, Vehicle, 50 mg/kg WHI-P131 [NP]) with 65 target tumors, 17 WHI-P131 [NP] (100-150 mg/kg)-treated mice with 38 target tumors, 20 gefitinib-treated mice with 28 target tumors, 34 gemcitabine-treated mice with 47 target tumors, and 27 paclitaxel-treated mice with 41 target tumors. The depicted results demonstrate a significant decrease in tumor volume and arrest of tumor growth for WHI-P131 [NP] treated mice (normalized volumes: 0.77±0.04 on day 7, P=$7.5x10^{-9}$ and 0.70±0.06, on day 14, P=$1.5x10^{-7}$ (see Table 1) and continuation of growth for the other three drug treatments.

Discussion

Liposomal nanoparticle therapeutics containing cytotoxic agents may provide the foundation for potentially more effective and less toxic anti-cancer treatment strategies due to their improved pharmacokinetics, reduced systemic toxicity, and increased intratumoral/intracellular delivery [8,9]. Here we report the anti-cancer activity of a PEGylated nanoparticle formulation of GMP-grade WHI-P131 in the MMTV-neu transgenic mouse model of chemotherapy-resistant breast cancer. Notably, this therapeutic nanoparticle formulation of GMP-grade WHI-P131 was substantially more effective than the standard chemotherapy drugs paclitaxel, gemcitabine, and gefitinib against chemotherapy-resistant breast cancer in the MMTV/*Neu* transgenic mouse model. These findings demonstrate that the nanotechnology-enabled delivery of GMP-grade WHI-P131 shows potential for treatment of breast cancer.

Overexpression of ErbB2 (Her-2/neu) is associated with chemotherapy resistance and poor treatment outcome in breast cancer [10,29]. Chemotherapy resistance of ErbB2/$Her2^+$ breast cancer cells has been attributed to activation of phosphatidylinositol 3 kinase (PI3-Kinase)/AKT anti-apoptotic signaling pathway and amplified expression of the resistance-associated survivin protein [10,29]. Use of the humanized recombinant monoclonal antibody trastuzumab/Herceptin binding the extracellular domain of the ErbB2/HER-2 receptor results in decreased chemoresistance and improved treatment outcome of ErbB2/$HER\text{-}2^+$ breast cancer [17]. Our findings provide unprecedented evidence that the multifunctional tyrosine kinase inhibitor WHI-P131 is an active agent against chemotherapy-resistant EbB2/$HER\text{-}2^+$ breast cancer in the well-established MMTV-neu transgenic mouse model.

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Treatment Group	# of Mice	# of Tumors	Tumor Volume, mm^3 (Mean ± SEM)			T-test P-Value (*vs* Control)			Normalized Tumor Volume (Mean ± SEM)		T-test P-Value *vs* Control	
			Day 1	Day 7	Day 14	Day 1	Day 7	Day 14	Day 7	Day 14	Day 7	Day 14
A. Control	38	65	675 ± 60	750 ± 64	1095 ± 102	—	—	—	1.22 ± 0.06	1.86 ± 0.19	—	—
B. WHI-P131[NP]	17	38	1004 ± 98	755 ± 89	666 ± 86	0.006	0.969	0.002	0.77 ± 0.04	0.70 ± 0.06	$7.5x10^{-9}$	$1.5x10^{-7}$
C. Chemo	81	116	518 ± 32	635 ± 39	748 ± 46	0.023	0.125	0.003	1.30 ± 0.05	1.57 ± 0.07	0.266	0.155
C.1 Taxol	27	41	526 ± 51	673 ± 57	788 ± 71	0.059	0.366	0.015	1.47 ± 0.10	1.72 ± 0.12	0.033	0.516
C.2 Gemcitabine	34	47	563 ± 59	690 ± 72	803 ± 81	0.184	0.531	0.027	1.26 ± 0.09	1.58 ± 0.12	0.634	0.211
C.3 Gefinitib	20	28	433 ± 47	487 ± 62	599 ± 83	0.002	0.004	$3.0x10^{-4}$	1.12 ± 0.08	1.35 ± 0.11	0.351	0.020

Table 1: Anti-Cancer Activity of WHI-P131 Nanoparticles in the MMTV/*Neu* Transgenic Mouse Model of Metastatic $HER2^+$ Breast Cancer. WHI-P131 [NP] (100 mg/kg or 150 mg/kg) was administered i.p. daily for 5 consecutive days each week, x 2 weeks; Taxol (6.7 mg/kg) was administered i.p. on days 1,3, and 5; Gemcitabine (33.7 mg/kg) was administered i.p on days 1 and 8; Gefinitib (75 mg/kg) was administered daily by gavage. Control group included mice that were treated with i.p. injections of WHI-P131-free vehicle, WHI-P131 [NP] at the suboptimal 50 mg/kg dose level, or PBS.

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