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Sonidegib, a Smoothened Inhibitor, Promotes Apoptosis and Suppresses Proliferation of Natural Killer/T-Cell Lymphoma

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Background: Dysregulation of the Hedgehog (Hh) pathway modulates various aspects of hematologic and solid tumors, but its effects in human Natural killer/T-cell lymphoma (NKTCL) are unclear. Moreover, no study has examined the consequences of pharmacologically inhibiting Hh signaling in NKTCL cell lines.

Material/Methods: In this study, the expression of Smoothened (Smo) and Glioma-associated oncogene 1 (Gli1) in NKTCL tissue were scrutinized. Two human NKTCL cell lines, SNK6 and SNT8, were subjected to various doses of sonidegib (a Smo inhibitor) and incubated for distinct durations. The cell apoptosis was examined by flow cytometry, CCK-8 assay was run to assess proliferation, and protein levels were quantified by Western blotting.

Results: Both Smo and Gli1 expression were higher in NKTCL tissue than in Lymphoid Reactive Hyperplasia (LRH). Sonidegib significantly suppressed proliferation in NKTCL cells and the effect was dose-dependent. Further analysis revealed that sonidegib treatment elevated the number of apoptotic cells in a dose- and time-dependent manner. In addition, sonidegib downregulated Smo and Gli1expression in NKTCL cells.

Conclusions: The Hh pathway is crucial to the development of NKTCL and thus holds huge promise as a treatment for this disease.

MeSH Keywords: Apoptosis • Hedgehogs • Natural Killer T-Cells

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Background

NKTCL, which is more common in Asian than in Western countries, is an aggressive non-Hodgkin lymphoma type with poor clinical outcomes [1,2]. It is the most frequently diagnosed type of mature T/NK-cell neoplasms in China, and is the second most common subtype, after diffuse large B-cell lymphoma, of all lymphoid neoplasms subtypes [1,3]. There is no standard treatment strategy for NKTCL patients. Because of the overexpression of multidrug-resistant genes, anthracycline-based chemotherapy is poorly effective [4]. Application of radiotherapy has greatly improved the prognosis of early-stage NKTCL [5]. Some studies have reported that NKTCL patients with refractory or relapsed disease benefit from receiving an L-asparaginase-containing regimen [6,7], but at relapse or advanced stage, patients with NKTCL have sub-optimal outcomes. Thus, novel treatments are needed for NKTCL.

The Hh pathway is essential for embryonic development [8]. Statistics indicate that about 25% of all cases of cancer-related mortality show signs of abnormal Hh signaling [9]. Dysregulation of this pathway leads to hematologic malignancies, including acute leukemia [10–12], chronic myeloid leukemia [13], chronic lymphocytic leukemia [14,15], lymphoma [16], and multiple myeloma [17]. Meanwhile, the Hh pathway modulates the functions of leukemia stem cells, which have been reported to be an important cause of chemo-resistance and relapse of cancers [8,18,19]. For this reason, blockade of Hh signaling may prevent hematological malignancies.

The Hh signaling is initiated by binding of 3 Hh ligands: Desert hedgehog (Dhh), Indian hedgehog (Ihh), and Sonic hedgehog (Shh). In its inactive form, the 7-transmembrane protein Smo is inhibited by a 12-transmembrane protein called Patched (Ptch) in the absence of Hh [20]. Binding of Hh ligand to Ptch activates Hh signaling, which relieves Smo inhibition, thereby activating nuclear localization of Gli1. Gli1 then activates tumorigenesis-associated genes (e.g., Bcl-2, Myc, Cyclin-D1, SNAIL, and SOX2) [21].

A number of Hh signaling pathway inhibitors are currently under clinical development, specifically for Smo, the key receptor involved in this pathway. As a result, sonidegib, which is a specific inhibitor of Smo, was approved by the FDA for basal cell carcinoma (BCC) in 2015. The present study explored the dysregulation of the Hh pathway in NKTCL patients and the impact of sonidegib on apoptosis and proliferation of NKTCL cell lines.

Material and Methods

Clinical data and treatment

Clinical characteristics and tumor specimen were harvested from 30 patients – 18 males and 12 females – from 2011 to 2018 at the First Hospital of Quanzhou Affiliated to Fujian Medical University. The WHO classification of lymphoid neoplasms was applied for patient selection [22]. The use of specimens was approved by the Regional Ethics Committee of the First hospital of Quanzhou Affiliated to Fujian Medical University.

Determination of Smo and Gli1 expression in human NKTCL tissue by immunohistochemistry (IHC)

Paraffin-embedded specimens were obtained from 30 individuals with newly diagnosed NKTCL and 10 individuals with LRH between 2011 and 2018 at the First Hospital of Quanzhou Affiliated to Fujian Medical University. The sampled were subjected to IHC staining assay utilizing the following polyclonal antibodies: anti-Smo (1: 100) and anti-Gli1 (1: 150) (Abcam, Cambridge, UK). We then counted all tumor cells and Smo or Gli1 staining tumor cells using a microscope (×400) in 4 fields. The percentage score was determined by the average percentage of tumor cells with positive staining: 0 (<10%), 1 (11–20%), 2 (21–50%), 3 (51–75%), and 4 (>76%). The intensity score depended on the staining intensity: 0 (negative), 1 (weak brown), 2 (brown), and 3 (strong brown). The level of Smo or Gli1 expression was obtained by multiplying percentage score and intensity score, divided into 4 groups: negative (–) (0), positive (+) (1–3), positive (++) (4-7), and positive (+++) (8–12).

Cell culture and cell lines

Human NKTCL cell lines SNK6 and SNT8 (Leeyond Technology Co., Xiamen, China) were cultured in RPMI-1640 (Thermo Fisher Scientific, Inc., Shanghai, China) medium mixed with 200 U/ml IL-2 (Sigma-Aldrich, USA), 100 U/ml penicillin/100 µg/ml streptomycin (HyClone, Utah, USA), and 10% FBS (Cellmax, Beijing, China) in a humidified incubator at 37°C with 5% CO_2. We replaced the cell medium every 2–3 days. NKTCL cells in logarithmic growth phase were used for the following experiments. Human peripheral blood mononuclear cells (PBMC) were isolated from a healthy volunteer.

Proliferation detection with CCK-8

Cells in logarithmic growth phase were grown on 96-well plates (1×10^4 cells/well). Thereafter, 200 ul sonidegib (Selleck Chemicals, Houston, USA) at concentrations of 0, 5, 10, 20, 30, 40, and 50 µM was added to the wells. Cells of the control group were treated with an equivalent volume of DMSO

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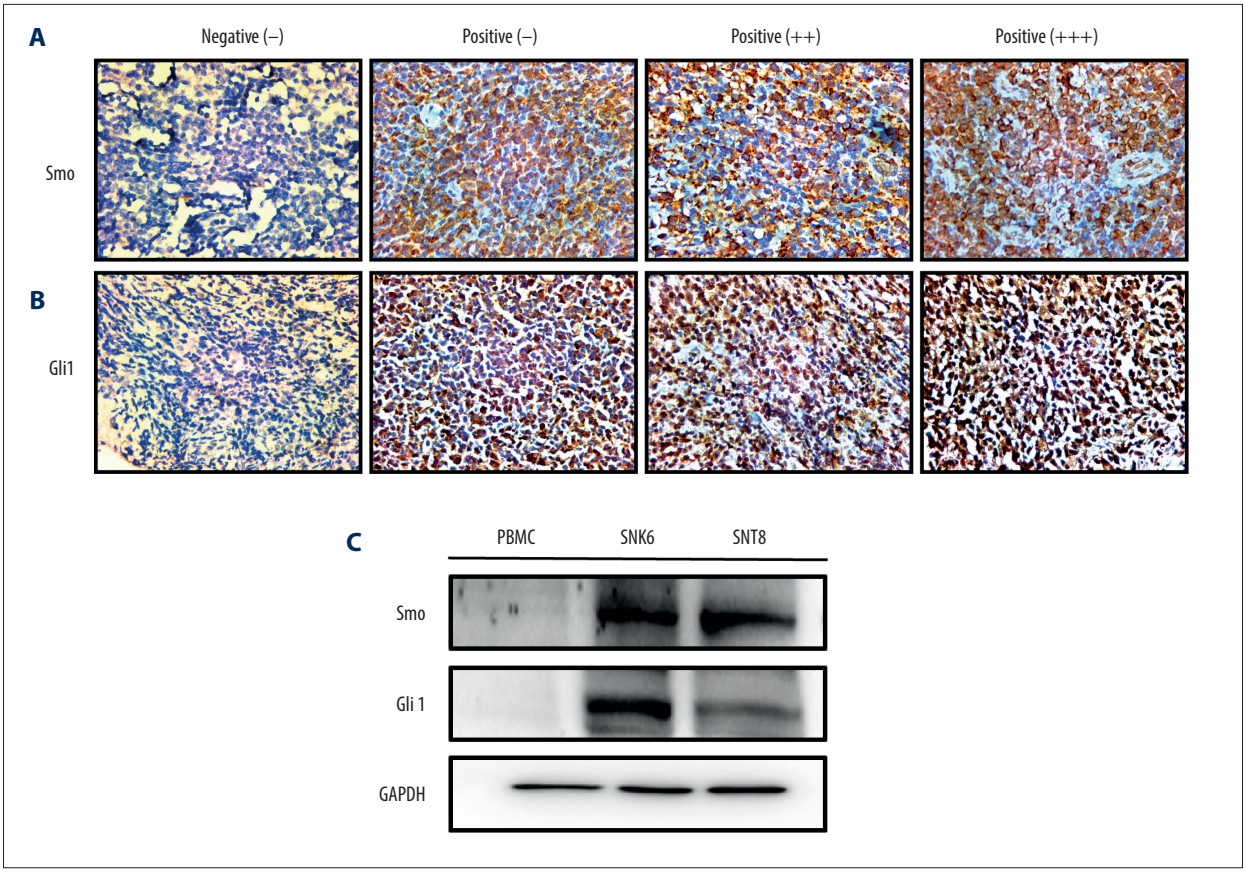

Figure 1. Smo and Gli1 expression in human NKTCL tissue and NKTCL cell lines. (**A**) Smo expression in NKTCL tissue by IHC. (**B**) Gli1 expression in NKTCL tissue by IHC. (**C**) Smo and Gli1 protein expression in PBMC, SNK6 and SNT8 cells.

Table 1. Smo and Gli1 expression in human NKTCL tissue.

		Total n	n				Positive (%)	Z	P
			–	+	++	+++			
Smo	NKTCL	30	10	12	5	3	66.7	–3.396	0.001
	LRH	10	10	0	0	0	0		
Gli1	NKTCL	30	8	10	6	6	73.3	–2.755	0.006
	LRH	10	8	1	1	0	20		

Table 2. Correlation between Smo and Gli1 expression in human NKTCL tissue.

		Gli1				rs	P
		–	+	++	+++		
Smo	–	7	1	1	1	0.618	0.0003
	+		8	4			
	++	1	1	1	2		
	+++				3		

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Table 3. Smo, Gli1 expression in human NKTCL tissue and their association with clinical parameters.

Parameters	Total (n)	Smo				P	Gli1				P
		–	+	++	+++		–	+	++	+++	
Gender											
Male	18	6	7	3	2	0.911	5	5	5	3	0.981
Female	12	4	5	2	1		3	5	1	3	
Age											
<60 y	18	5	7	3	3	0.244	4	5	4	5	0.188
≥60 y	12	5	5	2	0		4	5	2	1	
ECOG											
0–1	29	9	12	5	3	0.222	8	10	5	6	0.472
≥2	1	1	0	0	0		0	0	1	0	
Ann arbor											
I–II	26	8	11	4	3	0.540	6	10	5	5	0.800
III–IV	4	2	1	1	0		2	0	1	1	
B symptoms											
No	22	7	7	5	3	0.215	6	7	4	5	0.846
Yes	8	3	5	0	0		2	3	2	1	
LDH											
≤245 U/L	25	7	11	4	3	0.251	7	8	5	5	0.862
>245 U/L	5	3	1	1	0		1	2	1	1	
EBER											
Negative	6	3	2	1	0	0.310	4	2	0	0	0.010
Positive	24	7	10	4	3		4	8	6	6	
IPI score											
0–1	22	6	9	4	3	0.173	5	8	4	5	0.527
>2	8	4	3	1	0		3	2	2	1	
PINK score											
0–1	26	8	11	4	3	0.540	6	10	5	5	0.800
>2	4	2	1	1	0		2	0	1	1	

in place of sonidegib, and a zero-adjustment group was also set up. We then added 10 ul of CCK solution to the cells after 24 h, 48 h, or 72 h, after which the cells were cultured for 2 h at 37°C. The cell culture plate was placed in a microplate reader to read the absorbance at 450 nm. Cell viability (%)=(Absorbance of cells treated with sonidegib-absorbance of zero adjustment)/(Absorbance of control-Absorbance of zero adjustment)×100%.

Apoptosis detection by flow cytometry

Cells were treated with 0, 10, or 30 μM sonidegib for 24 h or 48 h, then collected and washed twice with binding buffer, and we adjusted the concentration to 5×10^5~10^6 cells/ml. Cell apoptosis was assessed using the Annexin V-FITC/PI kit (BD Biosciences, USA). Cells were resuspended in 500 μl binding buffer, mixed with 5 μl Annexin V-FITC, and then we added 5 μl propidium iodide (PI). Cells were subsequently incubated

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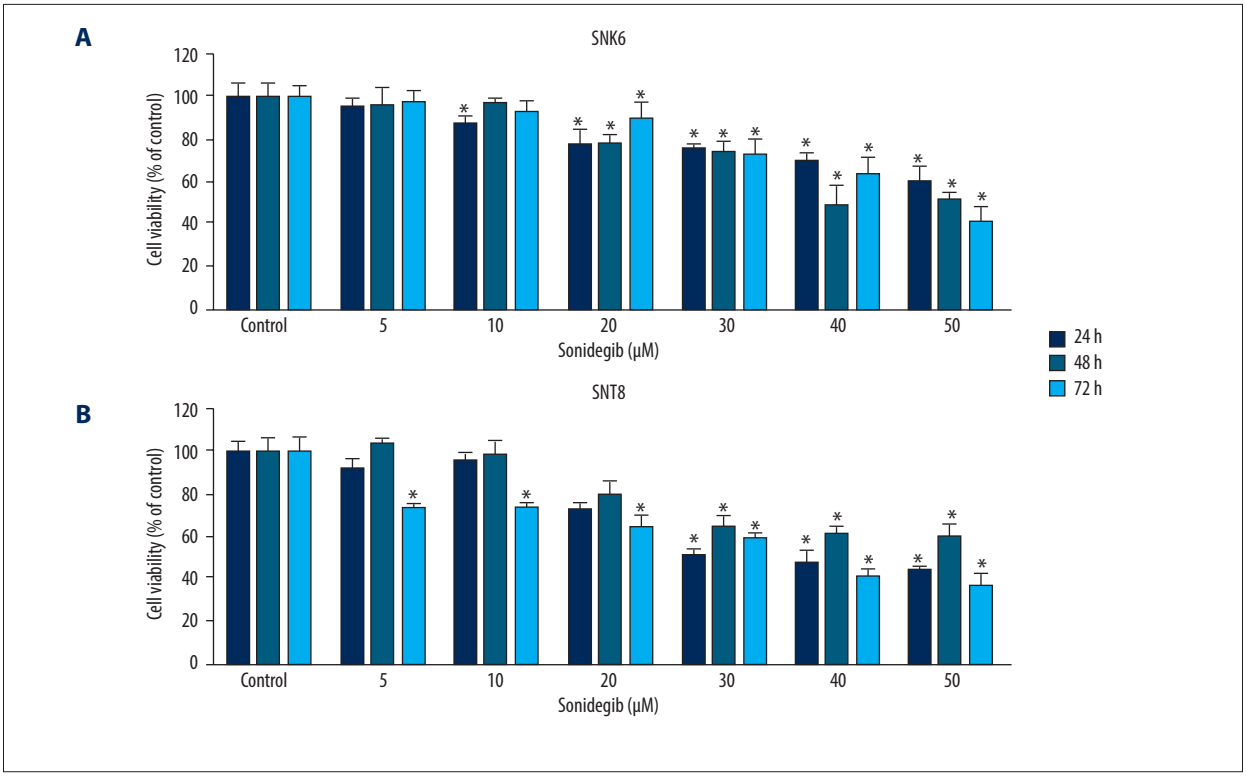

Figure 2. Sonidegib suppressed the proliferation in NKTCL cell lines. (**A**) SNK6 cells were incubated with increasing doses of sonidegib for 24, 48, or 72 h and then treated with CCK-8. (**B**) SNT8 cells were incubated with increasing doses of sonidegib for 24, 48, or 72 h and then treated with CCK-8. * P<0.05, relative to the control group.

at 25°C in the dark for 15 min. Apoptosis detection was performed by flow cytometry (BD Biosciences, USA) within 1 h.

Western blot analyses

Cells were treated with 0, 10, 20, or 30 μM sonidegib for 48 h. Thereafter, they were washed with PBS followed by treatment with lysis buffer (pH 7.0) mixed with protease inhibitor. The BCA Protein Assay kit (Beyotime, Jiangsu, China) was used to determine protein concentration in the lysates. Subsequently, the protein samples were separated by SDS-PAGE gel electrophoresis, followed by electrotransfer to PVDF membranes before they were immunoblotted with the antibodies against Smo and Gli. Antibodies against GAPDH (Beyotime, Jiangsu, China) served as the loading control. The PVDF membranes were treated with secondary antibody (anti-rabbit) and we used the enhanced chemiluminescence system to visualize the protein bands.

Statistical analyses

The fluorescence intensity of Smo and Gli1 between groups was compared by the non-parametric test with grade data. Intergroup comparisons were carried out by the Mann-Whitney U test. The correlation between Smo and Gli1 expression was performed by Spearman rank correlation. Quantitative data are presented as mean±SD. Differences between groups in terms of proliferation and apoptosis were determined by one-way ANOVA. A P-value <0.05 represented statistical significance. All analyses were performed using SPSS software, version 24.0 (SPSS, Inc., Chicago, IL, USA).

Results

Smo and Gli1 were highly expressed in human NKTCL tissues

We retrospectively evaluated Smo and Gli1expression in 30 NKTCL tissues (Figure 1, Table 1). We found positive Smo and Gli1 expression in 66.7% (20/30) and 73.3% (22/30) of NKTCL specimens, respectively, while there were 0% (0/10) Smo expression and 20% (2/10) Gli1 expression in LRH specimens. Positive stainings of Smo were mainly localized in the cell membrane and cytoplasm, while positive stainings of Gli1 were mainly localized in the cytoplasm and nucleus. In addition, Smo expression levels were positively correlated with those of Gli1 (Table 2).

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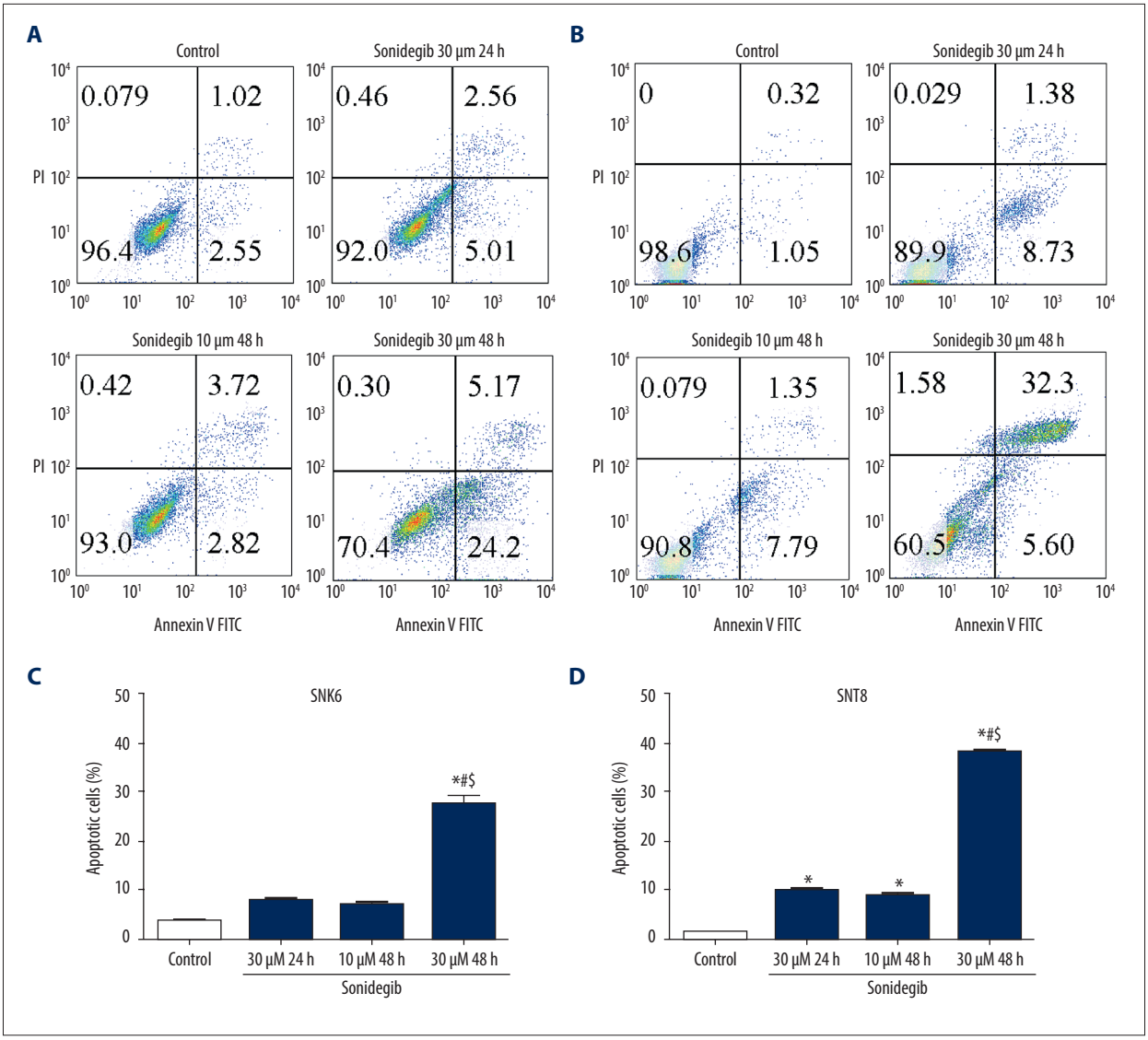

Figure 3. Sonidegib promotes apoptosis in NKTCL cell lines. (**A**) SNK6 cells were incubated with increasing doses of sonidegib for 24 or 48 h and analyzed by flow cytometry using propidium iodide and annexin V staining tests. (**B**) SNT8 cells were incubated with increasing doses of sonidegib for 24 or 48 h and analyzed by flow cytometry using propidium iodide and annexin V staining tests. (**C**) Effect of sonidegib on the apoptosis of SNK6 cells. (**D**) Effect of sonidegib on the apoptosis of SNT8 cells. * P<0.05, relative to control; $_{\#}$ P<0.05, relative to the group of sonidegib 30 μM 24 h; $_{\$}$ P<0.05 relative to the group of sonidegib 10 μM 48 h.

Gli1 expression was correlated with EBER in NKTCL patients

We analyzed the correlation between Smo/Gli1 expression and the clinical characteristics of NKTCL to explore the effect of Smo/Gli1 in NKTCL progression. Table 2 shows that Smo expression was not significantly correlated with clinical characteristics. However, overexpression of Gli1 was significantly associated with EBV-encoded RNA (EBER) (P<0.05, Table 3).

Sonidegib suppressed NKTCL cells proliferation

Figure 2 shows that the cell viability of NKTCL cell lines (SNK6 and SNT8) was decreased as the concentration of sonidegib increased. The suppression of NKTCL cells induced by sonidegib treatment was dose-dependent.

Sonidegib promoted apoptosis in NKTCL cells

Compared with control, the apoptotic cells were markedly elevated following treatment with 10 μM or 30 μM sonidegib

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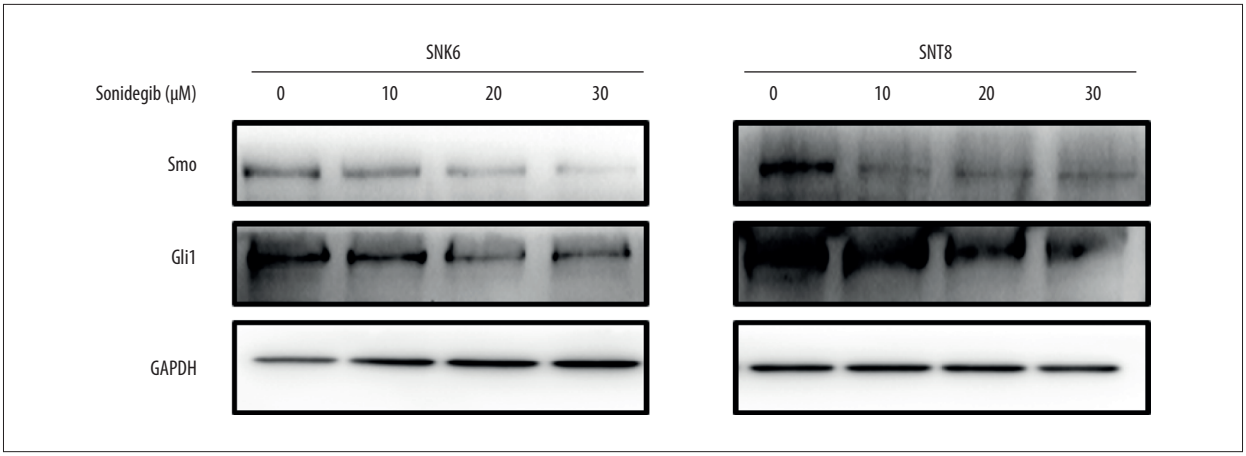

Figure 4. Smo and Gli1 expression in NKTCL cell lines treated with Sonidegib.

for 24 h or 48 h (P<0.05, Figure 3). Moreover, the number of apoptotic cells markedly increased following incubation with 30 μM sonidegib for 48 h compared to those incubated for 24 h (P<0.05, Figure 3), and the level of apoptosis at 30 μM sonidegib was higher than that of 10 μM sonidegib for 48 h (P<0.05, Figure 3). Promotion of apoptotic NKTCL cells induced by sonidegib treatment was dose- and time-dependent.

Sonidegib downregulated Smo and Gli1 expression

Hh signaling pathway protein expression after exposure to different concentrations of sonidegib is shown in Figure 4. Smo and Gli1 expression were obviously reduced by sonidegib in NKTCL cells (SNK6 and SNT8). Furthermore, increasing the dose of sonidegib significantly enhanced this effect, indicating the inhibitory effect was influenced by the dose. Our findings show that Hh signaling pathway can be suppressed by sonidegib through downregulation of Smo and Gli1 expression in NKTCL cells.

Discussion

Despite improvements achieved through L-asparaginase-containing regimen, patients with advanced-stage or relapsed NKTCL usually have a poor prognosis. Thus, the development of effective strategies to treat NKTCL is urgently needed. This is the first study showing dysregulation of the Hh signaling pathway in NKTCL. We first measured Smo and Gli1 expression in human NKTCL tissue by IHC. Results showed that both Smo and Gli1 expression were highly expressed in NKTCL tissue. Moreover, results showed a correlation between Smo and Gli1 expression in NKTCL, suggesting dysregulation of Hh signaling in NKTCL might be in a canonical activation manner. In addition, we used sonidegib to inhibit Hh signaling pathway in 2 NKTCL cell lines. Based on the NKTCL cell proliferation tests, results revealed that sonidegib effectively suppressed proliferation and this effect was influenced by the dose. Similarly, analysis of cell apoptosis demonstrated that sonidegib treatment enhanced apoptosis in a dose- and time-dependent manner. Moreover, Smo and Gli1 expression were downregulated by sonidegib. These results suggest the potential therapeutic effect on NKTCL by targeting the Hh signaling pathway.

Several studies have reported abnormal Hh signaling in various hematologic malignancies. Liang et al. [10] found that the Hh signaling pathway was upregulated in refractory/relapse acute myeloid leukemia patients. In a T-cell acute lymphoblastic leukemia study reported by Dagklis et al., activation of the Hh pathway was found in 20% of samples [11,12]. In a chronic myeloid leukemia study, the kinetics of Hh signaling activity during the individual medical history correlated with BCR-ABL1 mRNA level and with upcoming molecular relapse [13]. Additionally, Dagklis et al. [11]also showed that short interfering RNA-mediated knockdown or drug inhibition of Gli1 or Smo in T-ALL cell lines reduced cell proliferation. Furthermore, other scholars have reported that the Hh pathway is critical for maintaining of leukemia stem cells [18]. Inhibition of the Hh pathway reduces proliferation and renewal of stem cells, thus providing a potential mechanism for eliminating leukemia stem cells [19].

Recent years have witnessed an increase in studies aimed at developing drugs targeting the Hh signaling pathway, especially Smo, a G-protein-coupled receptor-like molecule which modulates Hh signaling. A number of Smo blockers have been studied in various types of cancers. Sonidegib and Vismodegib were approved by the US FDA for basal cell carcinoma [23,24], while glasdegib was approved for use in combination with low-dose cytarabine to treat acute myeloid leukemia [25]. Most Smo inhibitors bind to and inhibit Smo [21]. It was also reported that sonidegib inhibited cell viability and apoptosis *in vivo* and *in vitro* [17,26]. Elsewhere, in a murine model of chronic myeloid leukemia, treatment with sonidegib promoted

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the survival and decreased the progression of leukemia in secondary transplants [27]. Moreover, Smo deletion suppressed the number of leukemic stem cells [18].

The results discussed above imply that inhibiting the Hh pathway may be an attractive approach for treating hematologic malignancies. In addition to direct Smo inhibitors, studies are underway to design other inhibitors of the Hh pathway (e.g., Shh monoclonal antibody and Gli inhibitors GANT-61) [21].

The present study has revealed dysregulated Hh signaling in NKTCL, and its important role in NKTCL cell proliferation and tumorigenesis. Inhibiting the Hh signaling with sonidegib suppresses proliferation and promotes apoptosis in NKTCL, indicating it is a promising treatment for NKTCL. However, we did not directly silence Smo, which is a limitation of this study. Therefore, further detailed studies are needed to increase the clinical utility of current Hh inhibitors in NKTCL.

Conclusions

Smo and Gli1 are key players in the development of NKTCL. Sonidegib was shown to promote apoptosis and suppress NKTCL cell proliferation by downregulating Smo and Gli1 expression. Therefore, blockade of the Hh signaling by sonidegib could be an effective treatment for NKTCL.

Conflicts of interest

None.

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