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Targeting of the Hedgehog Signaling Pathway in Cancer Treatment

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ABSTRACT

The Hedgehog (Hh) signaling pathway is a developmental pathway that is highly conserved evolutionarily. While typically only displaying high activity during embryogenesis, overactivation of the Hh pathway in adults has been linked to multiple forms of cancer including acute myeloid leukemia, myelofibrosis, basal-cell carcinoma, pancreatic ductal adrenal carcinoma, and triple negative breast cancer. The prevalence of Hh activation in many different cancers has made it a prime target for inhibition of these cancers through novel therapies. This literature review sought to assess the current state of cancer treatment through inhibition of Hh signaling. Most current clinical trials involving the pathway use Smoothened (SMO) antagonists to limit GLI1 production and ultimately inhibit Hh signaling. Currently, the FDA has approved the use of the SMO antagonists vismodegib, sonidegib, and glasdegib for cancer treatment. While only these small molecule inhibitors of Hh signaling have been approved for cancer treatment at this point, inhibition of the Hh signaling has shown to be a promising avenue for novel cancer therapies, particularly for future treatment of basal-cell carcinoma.

KEYWORDS: Sonic, Hedgehog, Cancer, Glasdegib, Sonidegib, Taladegib, Vismodegib

INTRODUCTION

The Hedgehog (Hh) signaling pathway is signal transduction pathway that is highly conserved evolutionarily[1]. The pathway plays a major role in the early development of both vertebrates and invertebrates. Hh signaling was first discovered and studied in the fruit fly *Drosophila melanogaster* in 1980[2]. The pathway was shown to function in establishing polarity of the fly body and forming appendages such as legs or antennae[3]. Drosophila larvae with mutant Hh signaling were said to resemble Hedgehogs. While Hh signaling levels are extremely high in embryogenesis, the pathway typically has low levels of activity in adult organisms1. It was not until 1993 that Hh signaling was observed in vertebrates. Since then, researchers have discovered that Hh signaling is also conserved in vertebrates, including humans. When activated in adult humans, the pathway plays a role in would healing and the maintenance of stem cells responsible for tissue repair[4]. However, overactivation of the Hh pathway is linked to tumorigenesis and the progression of various cancers including acute myeloid leukemia (AML), myelofibrosis (MF), basal-cell carcinoma (BCC), pancreatic ductal adrenal carcinoma (PDAC), and triple negative breast cancer[5-9]. The prevalence of Hh activation in many different cancers has made it a prime target for inhibition through novel therapies.

THE Hh PATHWAY

Ligands of the Hh pathway are secreted and can act as autocrine and paracrine factors[9]. In vertebrates there are three main Hh ligands: Sonic Hedgehog (SHh), Indian Hedgehog (IHh), and Desert Hedgehog (DHh)[10-12]. These ligands bind to the membrane receptor Patched 1 (PTCH1)[13]. Without bound Hh ligand, PTCH1 inhibits the action of a protein named Smoothened (SMO)[14]. SMO is constitutively active without the inhibition from PTCH1 and it is considered to be a positive Hh signaling pathway regulator since, it promotes the activation of the downstream components of this pathway when active[15]. After the Hh ligand is bound to PTCH1, SMO is uninhibited which then activates GLI1, which in turn drives the transcription of Hh target genes[16].

MECHANISMS FOR Hh PATHWAY OVERACTIVATION IN CANCER

There are four proposed mechanisms for the cause of overactive Hh signaling in different cancers (Types I, II, III, and IV)[17]. The Type I mechanism is ligand-independent and is caused by two main types of mutations in the Hh signaling pathway[18]. The first is a loss of function mutation for PTCH1, which causes SMO to be hyperactive. The second is a SMO activating mutation such as W535L (among others). Both of these

these mutations cause hyperactivation of the Hh pathway and, therefore, GLI1 without the presence of a Hh ligand. Patients with these mutations are at an extremely high risk of developing BCCs[19]. The Type II mechanism is ligand dependent and is caused by the overactivation of autocrine/juxtracrine Hh signaling[1]. The Type III mechanism is ligand dependent and relies on paracrine signaling. In this mechanism, tumor cells secrete Hh ligands which then bind to PTCH1 receptors on stromal tumor cells[20]. The stromal tumor cells then have their Hh signaling upregulated. This creates a feedback loop where, because of the upregulated Hh signaling, the stromal tumor cells secrete growth signals to the tumor cells, which cause the tumor cells to grow and differentiate. Finally, the Type IV mechanism is when cancer stem cells have their Hh signaling over activated by either paracrine or autocrine signaling[17]. This causes the cancer stem cells to divide and proliferate more rapidly, leading to tumorigenesis.

DRUGS USED TO INHIBIT Hh SIGNALING

Four of the main drugs that have been used to inhibit Hh signaling are: glasdegib, sonidegib, taladegib, and vismodegib[17]. All four drugs are small molecule inhibitors of SMO that bind SMO at drug-binding pockets specific to each inhibitor. The binding of each drug to SMO changes its confirmation and this change inhibits the activation of GLI1. Glasdegib was approved by the FDA in 2018 for treatment of AML in combination with low dose cytarabine (LDAC)[21].

Sonidegib was approved by the FDA in 2015 for the treatment of locally advanced BCC**.** It is also currently being tested to treat TNBC and advanced solid tumors in clinical trials[7,22,23]**.** Taladegib is currently being testing to treat advanced solid tumors, esophageal cancer, and colon cancer is ongoing clinical trials[17,24]**.** Finally, vismodegib was approved by the FDA in 2012 for the treatment of locally advanced and metastatic BCC[25]**.** It is also currently being tested to treat pancreatic cancer, colorectal cancer, prostate cancer, and breast cancer[17,26]**.**

TREATMENT OF AML

AML is a disorder of myeloid stem cells which most often has a late onset time in human life (although there are some pediatric cases of AML), with median age of diagnosis at 67 years[27]. Because of the late onset of this disease, most patients diagnosed with AML often have many comorbidities and cannot receive intensive chemotherapy treatment because of the risk involved. Because of this, older individuals with AML have traditionally been treated with low dose cytarabine and hypomethylating agents since they are much less aggressive. A '7 + 3' regiment of cytarabine + an anthracycline has been the most prescribed treatment for high-risk AML patients in the past[28]. In this treatment, cytarabine is continuously infused intravenously for 7 days, along with short infusions of an anthracycline for the first 3 days. This regiment is usually effective initially, with 50-80% of patients experiencing complete remissions, but 60-80% of patients end up relapsing after this initial response. The median overall survival (OS) was only 7.7 months from initiation of treatment so better treatments were needed[27].

Overactivation of the Hh pathway has been noted in chemotherapy-resistant myeloid leukemia cells[28,29]. It was also observed that inhibition of the Hh pathway significantly increased the sensitivity of the myeloid cells to the chemotherapy[29]. Cortes et. al sought to exploit these findings by combining the SMO inhibitor glasdegib with low dose cytarabine (LDAC) in a Phase II Clinical Trial to investigate if the combination could improve upon existing therapies[27]. The main goal of the trial (primary endpoint) was to increase the median OS. In the trial, patients were given either treatments of glasdegib and LDAC or LDAC alone and the results were compared. The trial showed a statistically significant improvement (49% increase) in OS for patients treated with both glasdegib and LDAC compared to patients treated with just LDAC. Also, rates of complete remission (CR) and complete remission with incomplete blood count recovery (CRi) were higher in the patients given the joint treatment[28].

Another important aspect of this study is that the combination of glasdegib and LDAC was well managed by the patients[27]. The elderly patients tolerated this treatment better than combinations of other SMO inhibitors and chemotherapy. Overall, the amounts of dysgeusia, muscle spasms, and alopecia were lower with glasdegib and LDAC than previous treatments. The promising results from this study and others led the FDA to approve treatment of AML with a combination of glasdegib and LDAC in November of 2018 for patients 75 and under[21].

TREATMENT OF TRIPLE NEGATIVE BREAST CANCER

There have been remarkable breakthroughs in breast cancer therapy through targeted drugs[7]. Novel drugs have been discovered which can selectively target certain oncogenic drivers such as HER2, progesterone receptor (PgR), or estrogen receptor (ER). Any breast cancer expressing these receptors can be selectively targeted and prolonged disease control can be achieved. Major issues arise however when a tumor does not express HER2, PgR, or ER. This is a condition known as triple negative breast cancer (TNBC). There are no effective target therapies to date for TNBC. Chemotherapy is the current standard treatment for TNBC, but survivability is poor. Most patients diagnosed with TNBC only live about a year[7].

One possible avenue for new treatment for TNBC is the Hh pathway, which has been increasingly shown to contribute to TNBC growth[30]. To investigate the potential therapeutic benefit of inhibiting the Hh pathway, Ruiz-Borrego et. al conducted a Phase I Clinical Trial to study the clinical activity of a sonidegib and docetaxel combination[7]. Docetaxel is one of the most commonly used and effective drugs to treat metastatic breast cancer[31]. The purpose of this trial was the establish the recommended Phase II dose (RP2D)[7]. Since this was only a Phase I trial and was hence, small in nature (12 participants total) , conclusions cannot be confidently drawn about the antitumor activity of the combination of sonidegib and docetaxel. However, the three patients who received the highest dose level (DL3) had the greatest benefit from the study. One patient experienced a CR and the other two had long-lasting disease stabilizations. DL3 was determined to be the RP2D[7]. The Phase II trial has not yet been completed but treatment of TNBC with sonidegib and docetaxel at DL3 seems to show some promise.

TREATMENT OF BCC

Almost 3 million cases of BCC are diagnosed each year, making it the most common cancer in the United States[32]. Most BCCs are cured by surgery, but the disease may advance to locally advanced/metastatic BCCs in which surgery is not advisable[33]. Abnormal Hh signaling is the key molecular driver in the progression of BCC and it is present is over 90% of BCCs[34]. The main Hh inhibitor that has been used to treat BCC is vismodegib[8]. The SafeTy Events in VIsmodEgib study (STEVIE) studied the safety and effectiveness of vismodegib in 1215 people in 36 countries for up to six years[33]. It is the largest study ever conducted in patients with BCC. STEVIE found 68.5% response rate in patients with locally advanced BCC and a 36.9% response rate in patients with metastatic BCC.

Prior to STEVIE there had been case reports of persistent adverse effects (AEs) as a result of vismodegib treatment[33]. STEVIE showed that most of the AEs that are commonly caused by vismodegib treatment (such as weight loss, ageusia, alopecia, and muscle spasms) that were present when treatment stopped resolved within 12 months of the treatment discontinuation. 12 months after treatment continuation, 3.4% of patients still experienced muscle spasms, 8.1% had alopecia, 1.5% had ageusia, 3.4% had dysgeusia, and 5.4% still had decreased weight. Additional review showed that most of these persistent symptoms were grade 1 (mild) in nature.

STEVIE was an incredibly important study not just because of its size, but also because it was representative of the real-word BCC population[33]. The median age of participants with locally advanced BCC was 72.0 years while the median age of patients diagnosed with locally advanced BCC in the United States is 68 years[33,35]. Other factors such as disease severity were also consistent between STEVIE and the real-world BCC population[33]. Because STEVIE was so representative of the real-world BCC population and it showed that vismodegib treatment produced promising results with only mild side effects, it indicates that treatment of BCC with vismodegib could be a viable treatment for the wider population.

Taladegib is also currently being investigated as a possible treatment for BCC. A phase I clinical trial by Bendell et. al found that, out of 47 patients with BCC, 22 patients experienced either a CR or partial remission (PR) as a result of treatment with taladegib[24]. This amounted to an overall response rate of 46.8%. 21 patients (44.7%) were reported as having stable disease at the end of the trial and only 1 patient had progressive disease. The study also included 37 cancer patients (of multiple histologies) that did not have BCC. None of these patients experienced a clinical response (CR or PR). 23 of them were found to have progressive disease and only 5 of them reported having stable disease, the rest were not assessed.

Another goal of this study by Bendell et. al was to determine if taladegib treatment would be effective in BCC patients that had previously been treated with vismodegib. A previous phase I trial by Danial et. al had found that BCC patients who had undergone vismodegib treatment previously were resistant to sonidegib treatment and saw no measurable improvement[36]. The Bendell et. al study found that both Hh-inhibitor naïve patients (patients who have never taken a Hh inhibitor for treatment) and those that had previously taken vismodegib, experienced clinical responses to the taladegib treatment[24]. Because the sample size of this study was small, there was not enough statistically significant data to draw definitive conclusions from this outcome, but it is promising, nonetheless.

TREATMENT OF PDAC

Pancreatic cancer is one of the most lethal diseases of the GI tract and is currently the fourth leading cause of cancer related deaths[37]. Pancreatic ductal adrenal carcinoma (PDAC) is the most common and lethal form of pancreatic cancer, with a 5-year survival rate of only 8%[38]. Hh signaling has been shown to be critical for tumor progression in patients with PDAC, with the pathway frequently being persistently activated[6]. When overactivated, Hh signaling promotes epithelial-mesenchymal transition of pancreatic cancer cells, increasing their invasiveness and motility[37]. Some preclinical studies in animal models had shown improved outcomes when combining Hh inhibitors and chemotherapy to treat PDAC[39,40]. A study by De Jesus-

Acosta et al. set out to test the efficacy of a combined treatment of vismodegib with the chemotherapy agents gemcitabine and nab-paclitaxel in patients with untreated metastatic PDAC[37]. Unfortunately, the combination of vismodegib and the chemotherapy agents did not produce any measurable benefit compared to treatment with chemotherapy alone (the typical treatment). This study showed a progression free survival (PFS) time of 5.42 months and an OS of 9.79 months. For comparison, a phase III clinical trial studying the now standard treatment of gemcitabine and nab-paclitaxel for PDAC showed a PFS of 5.5 months and an OS of 8.5 months[41].

Another study by McCleary-Wheeler et al. set out to determine if a combination of vismodegib and erlotinib, an epidermal growth factor receptor (EGFR) inhibitor, would be effective in treating metastatic PDAC[26]. This combination was considered because EGFR signaling has been shown to promote PDAC proliferation by activating GLI1 and an increase in EGFR expression in PDAC results in a more aggressive form of the cancer[42,43]; as previously mentioned, Hh signaling is critical to for PDAC tumor progression and is often overactivated in PDAC[6]. The McCleary-Wheeler et al. showed that the combination of the vismodegib and erlotinib treatment was generally well tolerated but was not effective in reducing PDAC[26]. Out of the 69 participants in this study, none of them produced a clinical response to the treatment. 13 patients in total reported SD for an overall disease control rate of 18.9%.

TREATMENT OF ADVANCED SOLID TUMORS

In an interesting study, the Japanese researchers in the Ueno et. al study set out to study the effectiveness of taladegib in treating advanced solid tumors from many different cancers[44]. Another primary goal of this study was to determine if the global recommended dose of 400 mg of taladegib would be tolerated as well in Japanese populations. This recommended dose of 400 mg was determined by the Bendell et. al study mentioned earlier[24]. The Ueno et. al study surveyed 19 different patients with 6 different cancers including: biliary tract cancer, gastric cancer, pancreatic cancer, malignant mesothelioma, BCC of the skin, and schwannoma[44]. None of the patients exhibited a CR and only 1 had a PR, making for a response rate of 5.3%. 4 other patients exhibited stable disease as a best response, giving an overall disease control rate of 26.3%. Interestingly, only 1 patient with BCC participated in the study and that patient exhibited the only clinical response to the taladegib treatment, backing up the findings of the Bendell et. al study[24,44].

Another major finding of this study was that the recommended global dose of 400 mg of taladegib was not well tolerated by the participants[44]. 33% of the participants taking the 400 mg of taladegib experienced a clinically significant adverse event such as a severe decrease in appetite or thrombocytopenia. There were no clinically significant adverse effects for either the 100 mg or 200 mg trial groups. The recommended dose determined from the Bendell et. al study was determined in a majority (94%) Caucasian population whereas the entire patient population in this study (Ueno et. al) was entirely Japanese[24]. This study by Ueno et. al backs up previous data that showed variations in responses to anticancer agents between Caucasian and Japanese populations[45].

Another study by Stathis et. al set out to determine the efficacy of treating advanced solid tumors with a combination of sonidegib and paclitaxel[22]. Out of the 12 patients involved in the study, 3 experienced clinical responses and another 3 reported stable disease, making for a response rate of 25% and an overall disease control rate of 50%. Out of the variety of cancer types surveyed in this study, the most encouraging results came from ovarian cancer patients. Out of 9 participants with advanced ovarian carcinoma, 2 had a PR and another 2 reported stable disease. Also, out of 5 ovarian cancer patients that were resistant to previous chemotherapy treatments, 2 were able to achieve stable disease. The combination of sonidegib and paclitaxel was tolerated well by the patients and no new toxicities were identified in this study.

The efficacy of sonidegib alone in treating solid tumors was studied by Kieran et al[23]. This study included both pediatric (N=60) and adult patients (N=16). The overall response rate for the pediatric participants was 3.3% (2/60) while the rate for the adults was 18.8% (3/16). However, 10 patients were found to have active Hh signaling through Hh biomarker measurements. Out of these 10 patients, all 5 of the clinical responses were observed (50%). Both of the pediatric patients who responded to the treatment reported CR after 9 months. 2 of the adults experienced CR and 1 experienced PR. All of the patients who were positive for Hh signaling had medulloblastoma (MB). A randomized phase III trial is currently underway to test this combination in patients with Hh positive MB.

This study by Kieran et al. also highlighted some potential risk in treating children with Hh signaling inhibitors[23]. Indian Hh signaling was known to be critical to bone development and a previous study by Kimura et al. showed that short term inhibition of the Hh pathway in mice to premature growth plate fusion and permanent defect in bone structure[23,46]. With these risks in mind, researchers closely monitored the effects on the growth plates of the pediatric patients. There were 3 bone related toxicities identified during this monitoring[23]. For instance, one pediatric patient had knee cartilage closure on day 56 of treatment and wrist cartilage closure on day 196. Another experienced a

narrowing of the epiphyseal plate of the phalanx on day 133 of treatment and a condensation in the growth plate on day 169.

CONCLUSION

The high frequency of the of overactive Hh signaling in numerous cancer types has caused it to be highly studied as a possible avenue for new cancer therapies. Most current clinical trials involving the pathway use SMO antagonists such as glasdegib, sonidegib, taladegib, and vismodegib to limit GLI1 production and ultimately inhibit Hh signaling. Currently, the FDA has approved the use of three SMO antagonists for treatment in two different cancers (vismodegib and sonidegib for BCC and glasdegib for AML). Results from the clinical trials reviewed in this paper show great promise in targeting Hh signaling for future cancer therapy. One particularly promising avenue of research is the use of taladegib in the treatment of BCC. Not only did the treatment produce an overall response rate of 46.8%, but Bendell et. al also found that the treatment was effective in patients who had previously been demonstrated to have resistance to vismodegib and sonidegib. This is an interesting phenomenon that warrants further research into the difference in mechanism between taladegib and vismodegib/sonidegib. Another interesting phenomenon was seen in the Ueno et. al study. It showed that the global recommended dose of 400 mg of taladegib for advanced solid tumors was not tolerated well in Japanese populations, whereas it was tolerated well in the majority Caucasian population in which the recommended dose was established. This finding supports previous data showing that there is a difference between the responses of anticancer agents in Caucasian and Japanese populations. It also suggests that there may be differences between recommended doses for Caucasians and other ethnic groups as well, which warrants further research. Finally, it is important to stress that targeting Hh signaling is not a 'magic bullet' for cancer therapy. Even though Hh signaling has been shown to be critical to the progression of PDAC, studies using vismodegib as a possible anti-cancer agent for PDAC showed the drug had little to no effect on PDAC progression. The Kieran et al. study showed that there may be great risk involved with treating pediatric cancer patients with Hh inhibitors. Overall, inhibition of Hh signaling has shown to be a promising avenue for novel cancer therapies. New research into the pathway does not appear to be the route to a 'cure' for cancer, but there are undoubtedly positive therapeutic opportunities to be derived from it.

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