骨髄異型性症候群および白血病に対する強力なエピジェネティック薬

骨髄異型性症候群および白血病治療目的の新たなDNAメチル化阻害薬のphase Iの良好な結果が得られた

Positive Phase I results for novel DNA methylation inhibitor to treat myelodysplastic syndromes and leukemia

体内におけるがん細胞の機能方法を安全に変化させる新たな強力なエピジェネティック薬が発見された可能性があるとのスタディ結果が2012年AACR学会で発表された。研究者らは、既存のエピジェネティック治療薬decitabineの改良型である新たなDNAメチル化阻害薬SGI-110を開発した。彼らは骨髄異型性症候群または白血病患者におけるSGI-110の生物学的有効用量および忍容性を確定するためにphase Iトライアル—従来の最大忍容用量トライアルデザインを用いたものとは異なる新たなアプローチ法—を施行した。ヒトを対象とした初めてのスタディにおいて、彼らは再発または難治性の中等度または高リスクの骨髄異型性症候群または白血病患者を、SGI-110を毎日5日間皮下注射する群または週1回の注射を3週間施行する群に無作為に割り付けた。これまでに66人の患者を組み入れた。その結果、SGI-110は注射部位の疼痛、好中球減少、血小板減少および貧血などの有害事象が認められたが、忍容性は良好であることが示された。さらに、データからSGI-110は半減期が長く臨床効果を生み出すことが示された。少なくとも2人の患者が寛解し、うち1人は完全寛解でありもう1人は部分寛解であった。

Full Text

As a result of collaboration between academic and pharmaceutical scientists, made possible by a Stand Up To Cancer research grant, researchers may have discovered a new, potent epigenetic drug that could safely alter the way cancer cells function within the body, according to data presented at the AACR Annual Meeting 2012, held March 31 - April 4 in Chicago.

The epigenetic code studied can be thought of as small tags that decorate DNA and provide instruction for how the body uses DNA, according to Jean-Pierre Issa, M.D., professor of medicine and director of the Fels Institute for Cancer and Molecular Biology at Temple University in Philadelphia, Pennsylvania. In patients with cancer, this code has become abnormal. DNA methylation inhibitors are drugs that try to normalize these tags and the code of cancer cells.

“I compare it to war and diplomacy,” Issa said. Traditional cancer drugs declare war on cancer cells by killing them. In contrast, DNA methylation inhibitors use “diplomacy” and try to alter cancer cells. “These drugs try to remind the cancer cell of its normal origin and proper behavior,” he said. “They remove these ‘tags’ and rewrite the instruction manual.”

Using Stand Up To Cancer’s grant model of collaborative research, Issa and colleagues worked with Astex Pharmaceuticals to develop SGI-110, a novel DNA methylation inhibitor that is a modified form of an existing epigenetic treatment, decitabine. According to Issa, decitabine currently has limited efficacy because it is quickly degraded in the body. SGI-110 has the potential to demonstrate prolonged drug exposure and improved efficacy through protection from degradation.

Issa and colleagues conducted a phase I trial to establish a biologically effective dose and tolerability of SGI-110 in patients with either myelodysplastic syndrome or leukemia — a novel approach that differs from traditional use of the maximum tolerated-dose trial design.

In the first-in-human study, researchers randomly assigned patients with relapsed or refractory intermediate- or high-risk myelodysplastic syndrome or leukemia to subcutaneous daily injections of SGI-110 for five days or to weekly injections for three weeks.

To date, Issa and colleagues have recruited 66 patients. Results indicated that SGI-110 is well tolerated, with local injection site pain, neutropenia, thrombocytopenia and anemia as observed adverse effects.

In addition, data revealed that SGI-110 has an extended half-life and produces clinical response. At least two patients have had disease remission, with one complete response and one partial response. Issa presented complete safety and efficacy results during the meeting.

“There have been some remarkable results in patients who have no options left to them,” Issa said. A phase II study will soon be under way to further explore SGI-110 doses. In addition, Issa and colleagues are beginning to design studies exploring the use of the drug in other, more common solid tumors such as lung cancer and breast cancer.

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