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A novel oral nucleoside prodrug in Phase 3 development as a treatment for hematologic malignancies

A Novel Oral Nucleoside Analogue

Sapacitabine¹ is an orally-available, nucleoside analogue drug that acts through a dual mechanism of action against cancer cells that is unique among drugs of its class. Sapacitabine is currently in “SEAMLESS”, a pivotal Phase 3 trial in front-line acute myeloid leukemia (AML) in elderly patients. Intensive chemotherapy does not benefit most patients aged 70 years or older with acute myeloid leukemia. Median survival by intensive therapy is only 4.6 months and is associated with a 4-week death rate of 26% and an 8-week death rate of 36%. These facts underscore the need for a better treatment regimen for this patient population.

In a Phase 2 randomized trial in patients aged 70 or older with AML sapacitabine treatment resulted in one year survival of 30%, overall response rate of 35%, including complete remission (CR) of 25% and median treatment duration in patients with CR exceeding 9 cycles.² In a pilot study of sapacitabine alternating with decitabine in elderly AML 30-day mortality from all causes was 4.5% and 60-day mortality from all causes was 9.5%. The overall response rate was 34.8.³ In patients aged 60 or older with myelodysplastic syndromes (MDS) 1-year survival was achieved in 29% to 35% of patients and median survival ranged from 217 to 236 days.⁴ Phase 2 evaluation of sapacitabine in patients with non-small cell lung cancer (NSCLC) as a second-line treatment and Chronic Lymphocytic Leukemia (CLL) are in progress.

Published findings show that cells with homologous recombination repair pathway defects are particularly sensitive to sapacitabine but not gemcitabine.⁵ Sapacitabine was shown in preclinical models to be superior to either gemcitabine (Gemzar®; Lilly) or ara-C, two widely used nucleoside analogues.⁶ Gemcitabine is indicated for the palliative treatment of certain solid tumors, but is not active in leukemias or MDS. Ara-C in combination with an anthracycline is indicated for the treatment of AML but is often not tolerated by elderly patients.

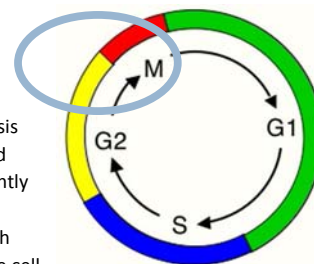
Sapacitabine is orally available. Nearly all available nucleoside analogue anticancer drugs must be administered by injection or continuous infusion.

The Cell Cycle

The cell cycle is comprised of a series of events culminating in cell growth and division. Check points along the cell cycle are used to detect and repair flaws in cell DNA that could lead to cancer cell proliferation. Nucleoside analogue drugs, like gemcitabine and sapacitabine, work by slowing down cell transit through different phases of the cell cycle, affecting the synthesis of DNA, arresting the cell cycle and forcing the cell into apoptosis or programmed cell death.

Mechanism of Action

Sapacitabine acts by a dual mechanism of action against cancer cells: it (a) interferes with DNA synthesis by first causing single strand breaks which are subsequently converted to double strand breaks resulting in cell death and (b) induces arrest of the cell cycle in predominantly G2/M-Phase and delays progression in S-Phase resulting in apoptosis.⁷



After administration, sapacitabine is converted into a metabolite called CNDAC. Both sapacitabine, as an oral prodrug, and CNDAC have demonstrated anticancer activity.

Clinical Results to Date

In a pilot study of sapacitabine alternating with decitabine in untreated AML patients aged 70 or older, 30-day mortality from all causes was 4.5% and 60-day mortality from all causes was 9.5%. The overall response rate was 34.8. An additional 26% of patients stayed on study for more than 4 cycles with a decrease in bone marrow blast counts despite not meeting criteria of response. Approximately 61% of patients received 4 or more cycles of the regimen.³

In a Phase 2 randomized trial sapacitabine was administered to 60 AML patients aged 70 or older who were either untreated or in first relapse. Sapacitabine was administered by 1 of 3 dosing schedules all in 3-4 week cycles: (A) 200 mg bid for 7 days, (B) 300 mg bid for 7 days and (C) 400 mg bid for 3 days for 2 weeks. Among the 3 schedules treatment with (C) resulted in 1-year survival of 30%, overall response rate of 35% and produced the highest complete remission rate of 25%. Median treatment duration in patients with CR exceeded 9 cycles.²

In a similar trial design conducted in patients aged 60 years and older with MDS who had progressed or relapsed after treatment with hypomethylating agents 1-year survival was achieved in 29% to 35% of patients and median survival ranged from 217 to 236 days across the 3 arms. Approximately 20% of all patients received sapacitabine for 4 to 6 cycles and 15% for 7 or more cycles. The mortality rate from all causes within thirty days of randomization was 6.6%.⁴



In a Phase 1 dose escalation clinical trial, reported at ASH 2007, sapacitabine was administered to 46 patients with advanced leukemias and MDS.

Complete remissions or complete remissions without platelet recovery were achieved in 6 patients. 15 patients had a significant decrease in bone marrow blasts, including 7 with blast reduction to 5% or less.^{8,9}

Sapacitabine is being investigated in the following clinical trials:

- elderly acute myeloid leukemia (AML), SEAMLESS pivotal trial **Phase 3**
- sapacitabine alternating with decitabine in elderly AML **Phase 2**
- non-small cell lung cancer (NSCLC) (*dose escalation stage*) **Phase 2**
- chronic lymphocytic leukemia (CLL) in patients with del11q22-23 **Phase 2**
- in combination with Cyclacel's oral CDK inhibitor seliciclib **Phase 1**

Sapacitabine completed clinical trials:

- elderly AML (n=60) and MDs as second line treatment (n=61) **Phase 2**
- cutaneous T-cell lymphoma (n=16) **Phase 2**
- advanced hematological malignancies (n=47) **Phase 1**
- advanced solid tumors (n=124) **Phase 1**

In a Phase 2 dose escalating trial sapacitabine was administered to 16 patients with cutaneous T-cell lymphoma after failure of at least one systemic therapy. Partial remissions were observed in three patients. Images from one such patient are shown below from baseline on December 3, 2008 (left), cycle 2 on December 22, 2008 (center) and cycle 4 on February 2, 2009 (right).¹⁰



Images courtesy of Dr. M. Duvic, MD Anderson Cancer Center.

In three Phase 1 dose escalation trials sapacitabine was administered to 124 patients with advanced solid tumors across various dosing schedules. Anti-tumor activity defined as stable disease over 4 months and tumor shrinkage was observed in 20 patients including 5 out of 18 with non-small cell lung cancer (28%), 4/40 colorectal (10%), 1/12 with breast (8%), 2/7 with ovarian (28%), 2/4 with bladder, 2/4 with GIST, 1/3 with renal, 3 with unknown primary and 1 each with small cell lung cancer and parotid tumors. Best response by investigator assessment was in a female patient with gastrointestinal stromal tumor or GIST refractory to imatinib who achieved stable disease for 50 months on sapacitabine treatment.¹⁰

In addition Phase 2 enrollment is ongoing in patients with NSCLC who progressed after receiving treatment with at least one platinum-containing regimen.

Combinations

Phase 1 enrollment is ongoing in patients with advanced solid tumors who are receiving treatment with a combination of oral sapacitabine and seliciclib, Cyclacel's orally-available CDK inhibitor.

At a poster presentation at the 2009 Congress of the European Hematology Association (EHA) Cyclacel scientists reported preclinical data supporting potential combinations of sapacitabine with novel targeted agents and other nucleoside analogues for the treatment of cancer.¹¹ The combinations exploit sapacitabine's unique mechanism of action and were shown to be effective in models of leukemia and solid tumors. The results showed robust synergy when sapacitabine was combined with inhibitors of cell cycle checkpoints, cell survival, and DNA repair, including targeted inhibitors of ATM, BCL-2, CHK1, DNA-PK and PARP. In addition, increased apoptosis or cancer cell death was observed when sapacitabine was administered in combination with other nucleoside analogs which inhibit ribonucleotide reductase, such as clofarabine and gemcitabine.¹¹ The findings extend previously reported data supporting the combination of sapacitabine with demethylating agents or HDAC inhibitors.¹²

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Pivotal Trial

Sapacitabine is currently in "SEAMLESS", a pivotal Phase 3 trial in front-line acute myeloid leukemia (AML). SEAMLESS is being conducted under a Special Protocol Assessment agreement with FDA and is chaired by Hagop M. Kantarjian, M.D., Chairman and Professor, Department of Leukemia, The University of Texas MD Anderson Cancer Center. SEAMLESS is a multicenter, randomized, Phase 3 study comparing three treatment arms. In Arm A sapacitabine is administered in alternating cycles with decitabine, in Arm B sapacitabine is administered alone and in Arm C decitabine is administered alone. The primary efficacy endpoint is overall survival. The study is designed to demonstrate an improvement in overall survival of either of two pairwise comparisons: (1) Arm A versus Arm C or (2) Arm B versus Arm C. Approximately 150 patients per arm or a total of 450 patients from approximately 50 centers will be enrolled. SEAMLESS will be monitored by a Data Safety Monitoring Board (DSMB). Two prespecified interim analyses for safety and futility will be performed and reviewed by the DSMB.

Endnotes:

- ¹ An experimental drug under clinical investigation. Not approved for human use.
- ² Kantarjian, H, et al, Abstract #1061, ASH Annual Meeting, December 2009, New Orleans, LA.
- ³ Ravandi et al 2011 J Clin Oncol 29 abs 6587
- ⁴ Garcia-Manero et al ASH Annual Meeting 2010 Abs 1857]
- ⁵ Liu, et al Blood 2010 116:1737-46
- ⁶ Wu et al, Cancer Research 2003;63:2477-82.
- ⁷ Hanaoka, K. et al, Int J Cancer, 1999;82:226-36 and Liu H. et al, Can. Res., 2005;65:6874.
- ⁸ Kantarjian et al. J Clin Oncol.2009; 0: JCO.2009.25.0209.
- ⁹ Plunkett, W., et al, Abstract 884, ASH 2007.
- ¹⁰ Cyclacel data on file.
- ¹¹ Frame, S., et al, Abstract 761, EHA 2009.
- ¹² Green, S., et al Abstract 4552, AACR 2009.

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For more information on sapacitabine trials, please visit the Cyclacel website at www.cyclacel.com or www.clinicaltrials.gov.

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