

Overview

Several nucleoside analogs are in routine clinical use for the treatment of cancer. Interest in the class of molecule remains high; three new nucleosides have received FDA approval with the past few years: cladribine, fludarabine, and gemcitabine. Gemcitabine (Lilly's Gemzar) had sales of over \$1 billion in 2005 and is projected to grow to \$2 billion by 2008.

Nucleoside analogs are effective in treating cancer because they mimic the natural nucleosides that are the building blocks of DNA and RNA. Cancer cells are 'fooled' into using these unnatural nucleosides for making DNA and/or RNA, resulting in inhibition of DNA or RNA synthesis. Cell division is inhibited and ultimately tumor cell death occurs.

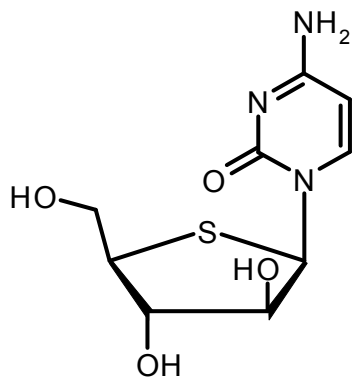
Small changes in the structure of nucleosides can have a profound effect on the anticancer properties of these compounds, and there has been extensive research into nucleosides to produce compounds with improved activity.

Thiarabine, developed by the Southern Research Institute and licensed to Access, was rationally designed for improved activity over cytarabine and gemcitabine.

In preclinical studies thiarabine exhibited significant activity in a wide variety of solid tumor xenograft models, and remarkable efficacy in the prevention and treatment of rheumatoid arthritis.

In two Phase I clinical studies, thiarabine has shown promising results in efficacy and safety in solid tumors.

Unique Mechanistic Profile of Thiarabine

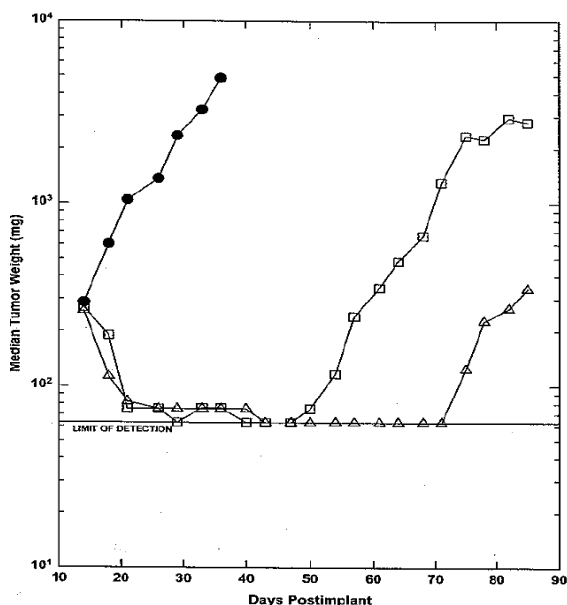


Structure of 4'-thio-araC

Thiarabine is 4'-thio arabinofuranosylcytosine, also known as 4'-Thio-ara-C, T-ara-C, SR-9025, and OSI-7836. The compound is similar in structure to ara-C, with the oxygen atom of the sugar ring replaced by a sulfur atom. Research work at the Southern Research Institute (Birmingham, AL) demonstrated thiarabine to be a potent molecule with beneficial spectrum of activity. The properties that may give thiarabine its greater anti-tumor activity in comparison to other drugs are:

- Long intracellular half-life
- Reduced susceptibility to inactivation by deaminases
- More potent inhibitor of DNA replication
- promotes cleavage of Caspase 3 and PARP leading to apoptosis and tumor cell death.
- inhibits kinase signal transduction pathways in endothelial cells and in vivo angiogenesis.

Summary of Results from Xenograft Experiments



This figure shows tumor growth inhibition of s.c. implanted CAKI-1 renal tumors in mice. Thiarabine was administered daily, 90mg/m²/dose, on days 14-22 (triangles) or 3 times a day at 30 mg/m²/dose, days 14-22 (squares) versus control (circles). The growth curves are only for mice with observable tumors. There were 4/6 cures in the group treated daily, and 2/6 in the group treated 3 times daily; 0/12 tumor-free survivors in the control group.

- Exhibited significant activity, including regressions and cures in 6 leukemia and lymphoma xenograft models
- Produced better activity than cytarabine in 4/6 of these models, and comparable activity in the other two models
- Performed better than gemcitabine in many solid tumor models. Unlike cytarabine, thiarabine was found to be active in a wide variety of solid tumor xenograft models (15 different tumor types), especially colorectal, lung, renal, prostate, breast and pancreatic tumors
- Activity also better than paclitaxel or cisplatin in certain lung models

Preclinical Studies in Rheumatoid Arthritis

Rheumatoid arthritis (RA) is an autoimmune disease with chronic joint inflammation, characterized by swelling of joints and destruction and erosion of bones. Angiogenesis is important in the pathogenesis of RA and has been recognized as a target for the treatment of RA. Access recently reported preclinical data demonstrating that thiarabine showed remarkable efficacy in the prevention and treatment of rheumatoid arthritis (RA). In a well-established animal model for RA, an exceptional restoration of joint structure was observed in the studies, which were conducted at Wayne State University School of Medicine and at Southern Research Institute.

Results of Prophylactic study

- Complete protection from onset of disease achieved at the 60mg/kg/day dose level and a significant reduction of disease at the 20 mg/kg/day dose level
- Significant reduction of number of paws affected and reduced severity in paws that did develop arthritis
- Marked reduction in pathological features of type II CIA (both inflammatory and erosive disease and protection of loss of cartilage matrix)

Results of Therapeutic study

- 100% of animals treated with 90mg/kg/day entered disease remission at some point and 60% maintained clinically disease free state at the conclusion of the study
- 70% of animals treated with 60mg/kg/day entered remission at some point in the study with 40% remaining in remission at the conclusion of the study.
- Significant reduction in disease score and number of involved paws at the 90 and 60mg/kg/day dose levels
- The reduction of all histological parameters of arthritis was highly significant.
- Restoration of joint structure observed at the 90mg/kg/day

Thiarabine Clinical Studies in Solid Tumors

- Two phase 1 studies were conducted of thiarabine monotherapy in patients with solid tumors.
- In the first phase 1 study, 26 patients with incurable advanced and/or metastatic solid tumors were enrolled. The protocol involved dose escalation, starting at 100 mg/m² iv over 30 minutes on days 1 and 8, every three weeks. Out of 21 evaluable patients, 9 experienced stable disease (median duration 4.3 months, range 1.8-6.4 months) . Dose-limiting toxicities (DLTs) were observed at 400-600 mg/m². Unlike previous observations with gemcitabine and cytarabine (where the DLT is myelosuppression; leucopenia and thrombocytopenia), there were no grade four toxicities and no hematological toxicities other than reversible, lymphopenia. OSI concluded that the (Grade 3) dose-limiting toxicities were fatigue, rash, fever, seizure and lymphopenia.
- A second solid tumor phase I trial was carried out to explore other schedules. The schedules were 200 mg/m² via 60-minute IV infusion every 21 days, 5-minute bolus on same schedule, and 5-minute bolus weekly for 4 weeks starting with a dose of 100 mg/m². Of the 27 evaluable patients, 7 patients (bladder cancer and mesothelioma) achieved disease stabilization (median 3.7 months, range 1.9-5.4). The main toxicity was fatigue, which appeared to be schedule independent.

Summary

- Thiarabine combines anti-proliferative and anti-angiogenic activity in one molecule for a dual mechanism of drug action to achieve the excellent in vivo efficacy against a number of solid tumors.
- Thiarabine demonstrated potent anti-arthritis activity in pre-clinical collagen II -induced arthritis mouse model.
- Consistent with Phase 1 clinical study, anti-inflammatory and anti-angiogenic cytokine IL-10 significantly elevated in mouse blood serum after the Thiarabine treatment.



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